The association between rhinitis and asthma of occupational origin

by

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Abstract

The present thesis explores the relationship between occupational rhinitis and occupational asthma under the postulates of the "united airways disease" concept that refers to the multiple links observed between rhinitis and asthma. Accordingly, the main objective of this thesis is to demonstrate the concomitant expression of significant changes in nasal patency and bronchial calibre following exposure to occupational agents during specific inhalation challenges, complementing the assessment with the investigation of changes in markers of airways inflammation in nasal lavage. To achieve the objectives, we set up a protocol to diagnose occupational rhinitis and conducted a study from January 2005 to January 2007 at Hôpital du Sacré-Coeur de Montréal in subjects undergoing investigation for occupational asthma. The reliability of the main research tools –acoustic rhinometry and nasal lavage- used to investigate occupational rhinitis was tested by analyzing the reproducibility of the methods. Both methods proved sufficiently reproducible to be included in our investigative protocol. The results presented in this thesis demonstrate a joint reaction of the nose and the lungs in a group of study subjects after performing specific inhalation challenge. This supports the concept of a "united airways disease" and its applicability to rhinitis and asthma of occupational origin. However, the results also show that although occupational rhinitis frequently coexists with occupational asthma it can also be present without occupational asthma. The assessment of upper airways inflammation in a subgroup of study subjects by the nasal lavage method allows us to observe significant changes in eosinophils counts after the challenge that correlates with the decrease in nasal patency observed in the same subjects.

Résumé

Le but de cette thèse est d'explorer la relation qui existe entre la rhinite professionnelle et l'asthme professionnel sous le postulat d'une "maladie unique de tout l'arbre respiratoire (united airway disease)", concept qui prend son origine dans les nombreux liens cliniques observés entre la rhinite et l'asthme. Plus précisément, cette thèse a comme objectif de démontrer de façon empirique la présence de changements concomitants dans la perméabilité nasale et dans le calibre des bronches lors de l'exposition à des substances allergènes d'origine occupationnelle. Un objectif complémentaire est de mesurer dans le lavage nasal les marqueurs de l'inflammation qui accompagnent la congestion nasale lors de ces expositions. Pour réaliser ces objectifs, nous avons développé un protocole de diagnostic de la rhinite professionnelle et mené une étude clinique de janvier 2005 à janvier 2007 à l'Hôpital du Sacré-Cœur de Montréal. L'observation des réactions nasales s'est faite lors de tests de provocation bronchique spécifiques visant à déterminer l'origine professionnelle de l'asthme. L'évaluation de la reproductibilité des techniques d'investigation – rhinométrie acoustique et lavage nasal– utilisées pour le diagnostic de la rhinite professionnelle a démontré que ces deux méthodes étaient suffisamment reproductibles pour être incluses dans notre protocole d'évaluation. Les résultats présentés dans cette thèse montrent que chez plusieurs sujets étudiés, il y avait une réaction concomitante dans le nez et les bronches, appuyant ainsi le concept du "*united airways disease*". Les résultats montrent également que même si la rhinite professionnelle coexiste souvent avec l'asthme professionnel, elle peut aussi être présente en son absence. La mesure des marqueurs d'inflammation dans le

lavage nasal montre des changements significatifs dans le nombre d'éosinophiles lors de la diminution de la perméabilité nasale.

Acknowledgments

As I sit down to write this section, I realize that this project has come to an end. Writing this thesis has been one of the greatest challenges of my life, weaving together several strands in my life and work. Many people have made enormous contributions to the successful outcome of this adventure. I would like to thank the people I feel have been particularly important in making this thesis possible.

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Lucero, Daniel and Juliana, you have been my joy and great strength in everyday life. This thesis is dedicated to you "con todo mi amor."

Roberto Castaño

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Preface

In compliance with McGill University requirements, I attest to the originality of this thesis as well as to the contributions of co-authors as outlined below.

Statement of originality

This thesis is based on studies conducted by the author at Hôpital du Sacré-Coeur de Montréal, Centre de Recherche/ Pneumologie during the period from January 2005 to January 2007. The studies presented within the thesis represent original research on occupational rhinitis. To my knowledge, this was the first time that a protocol was set up to systematically diagnose occupational rhinitis in a group of subjects undergoing investigation for occupational asthma and by so doing attempted to demonstrate a concomitant reaction of the nose and the lungs after exposure to occupational agents in the context of specific inhalation challenge. The results of the study provided objective evidence in support of the "united airways disease" model and its applicability to rhinitis and asthma of occupational origin. Additionally, to my knowledge, the reproducibility of the investigative tools used in this research for the investigation of occupational rhinitis (acoustic rhinometry and nasal lavage) was for the first time systematically examined in the setting of specific inhalation challenges with occupational agents.

The final part of this thesis presents original nosological considerations on the domain of occupational rhinitis by proposing a new definition and classification of this respiratory condition. These nosological considerations have already had an impact insofar as the international Task Force of the European Academy of Allergy and Clinical Immunology (EAACI) considered

them in the preparation of a recent position paper on occupational rhinitis that will be published in the near future.

Contribution of co-authors

The author of this thesis is the primary author of all the publications inserted in the thesis.

In the publications presented in Chapters1, 2 and 3, the author was responsible for:

- The conception and design of the studies
- Recruitment of patients and acquisition of data
- Collecting data
- Supervising data collection by the technician
- Editing, coding and entering the information from the tests performed for the studies
- Analysis and interpretation of data
- Drafting of all the manuscripts

In the publications presented in Chapters 4, 5, 6 and 7, the author was responsible for the conception and drafting of the articles.

Dr. Gilles Theriault contributed to the conception and design of the studies as well as the preparation, editing and critical review of the manuscripts of which he was co-author (Chapters 1, 2, 3, 5, 6 and 7).

Dr. Denyse Gautrin contributed to the conception, design and in situ supervision of the studies as well as the preparation, editing and critical review of the manuscripts of which she was co-author (Chapters 1, 2, 3 and 5).

Dr. Jean Luc Malo contributed to the conception, design and in situ supervision of the studies as well as the preparation, editing and critical review of the manuscripts of which he was co-author (Chapters 1, 2, 3 and 4).

Dr. Karim Maghni provided expertise in the development of the protocol for performing the nasal lavage technique described in Chapters 1 and 3 as well as the supervision of the analysis of the samples obtained by this method. He also provided a critical review of the manuscript presented in Chapter 3

Dr. Heberto Ghezzo helped with the statistical expertise and critical review of papers presented in Chapters 1, 2 and 3.

Research technician Carole Trudeau participated in the in situ work and measurements conducted in all the studies (Chapters 1, 2 and 3)

List of abbreviations

AR	acoustic rhinometry
ARIA	Allergic Rhinitis and Its impact on Asthma
BHR	bronchial hyperresponsiveness
CR	coefficient of repeatability
CV	coefficient of variation
DTT	dithiothreitol
ECP	eosinophilic cationic protein
FEV_1	forced expiratory volume in 1 second
HMW	high-molecular weight agent
ICC	intraclass correlation coefficient
ICR	International Consensus Report
IgE	Immunoglobulin E
LMW	low-molecular weight agent
MCA	minimum cross-sectional area
NAL	nasal lavage
OA	occupational asthma
OR	occupational rhinitis
PBS	phosphate-buffered saline
PRR	prevalence rate ratio
r	correlation coefficient
RADS	Reactive Airways Dysfunction Syndrome
RR	relative risk
RUDS	Reactive Upper Airways Dysfunction Syndrome
SD	standard deviation

SIC	specific inhalation challenge
TCC	total cell counting
UAD	United airways disease
Vol_{2-5}	nasal volume between 2 to 5 cm into the nose
95% CI	95% confidence interval

Introduction

Rhinitis and asthma are common coexisting respiratory conditions. The multiple links between rhinitis and asthma are nowadays referred to as the "united airways disease" concept in which upper and lower airways inflammation would influence each other. Current evidence from epidemiological studies indicates that this model would be applicable to rhinitis and asthma of occupational origin.

Occupational rhinitis and occupational asthma represent an excellent model for studying the interaction between rhinitis and asthma and for providing additional evidence in support of the "united airways disease" model. Yet there is a rising interest in the study of occupational rhinitis, which can be seen as an early stage of occupational asthma. Thus, if rhinitis and asthma are manifestations of a same disease in the upper and lower airways both may be investigated and objectively diagnosed following a similar and parallel diagnostic approach. With the means currently available to investigate and diagnose respiratory conditions it is possible to assess whether the nose and lungs may react concurrently in response to noxious agents. Presently, the investigation and diagnosis of occupational asthma is made by a widely accepted and standardized protocol that entails performing a specific inhalation challenge. However, occupational rhinitis appears to be underdiagnosed, and standardized criteria for investigating and diagnosing this condition using objective measurements of nasal patency and nasal airways inflammation are lacking.

Aim of the thesis

This thesis aims to provide a better understanding of the link between rhinitis and asthma by using occupational rhinitis and occupational asthma as a model

to characterize and demonstrate such an interaction. The main objective of this thesis is to:

- Demonstrate the concomitant expression of significant changes in nasal patency and bronchial calibre following exposure to occupational agents in the context of specific inhalation challenges.

Ancillary objectives are to characterize the inflammatory response of the nose to occupational agents by:

- Assessing changes in cellular markers of inflammation in nasal secretions after specific inhalation challenges;

and to assess the accuracy of the main research tools used in our study to investigate occupational rhinitis by:

- Evaluating the reproducibility of acoustic rhinometry during specific inhalation challenge;
- Evaluating the reproducibility of nasal lavage during specific inhalation challenge.

Outline of the thesis

This is a manuscript-based thesis. The central theme of this thesis has not been addressed in previously published work. The thesis is based on a series of empirical studies complemented and supported by some related theoretical articles written during the time interval the research project was carried out.

The background section gives an overview of the existing literature on the "united airways disease" concept. The core of the section describes the different types of evidence that support the link between rhinitis and asthma in

the general population as well as the scarce evidence available supporting the applicability of the "united airways disease" model in the workplace.

The thesis is further divided into four parts:

Part I addresses the investigation carried out to diagnose occupational rhinitis and occupational asthma. In **Chapter 1** (Occupational rhinitis in workers investigated for occupational asthma), the main study of the thesis is described. The central question in this chapter is whether someone who reacts to an occupational agent in the lungs during a specific inhalation challenge will react to the same challenge in the nose. The study design and investigative protocol made it possible to test the applicability of the "united airways disease" concept to work-related rhinitis and asthma. Although the study deals with the diagnosis of both occupational rhinitis and occupational asthma, it primarily focuses on describing the approach to investigating occupational rhinitis.

In achieving the objectives of this thesis, reliable investigative methods were essential but uncertain. In **Part II** the reliability of the main methods used to monitor nasal responses during the challenge protocol described in Chapter 1 is analyzed. Specifically, **Chapter 2** (Reproducibility of acoustic rhinometry in the investigation of occupational rhinitis) and **3** (Reproducibility of nasal lavage in the context of the inhalation challenge investigation of occupational rhinitis) reports the results of the assessment of the reproducibility of acoustic rhinometry and of the nasal lavage method, in the context of our study. In both studies, the results are discussed and a comparison is made with a selection of similar studies carried out by other investigators. **Part III** deals with some rhinitis and asthma management policy considerations. In **Chapter 4**

(Towards a united management of united airways disease: the role of otorhinolaryngologists and pneumologists), we consider the need to establish appropriate guidelines for the joint diagnosis and management of patients suffering from both rhinitis and asthma based on what we learned from our diagnostic approach while conducting the study presented in Chapter 1, as well as on the results obtained. **Part IV** comprises three studies dealing with nosological considerations on the definition and classification of occupational rhinitis. These theoretical considerations enabled us to put forward a new definition of occupational rhinitis that was used to define the cases for the main study. In **Chapter 5** (The definition of rhinitis and occupational rhinitis needs to be revisited) the problem with current definitions of rhinitis and occupational rhinitis is described and discussed. Consequently, in **Chapter 6** (Defining and classifying occupational rhinitis) we propose a new definition and classification of occupational rhinitis. In **Chapter 7** (Categorizing nasal septal perforations of occupational origin as cases of corrosive rhinitis) the approach to defining and proposing a particular type of occupational rhinitis classified in Chapter 6 is discussed. Finally, in **Chapter 8** (General discussion, implications and future perspectives) an integrated view of the results presented in Part I and II of this thesis is provided with a general discussion. Clinical and public-health implications from the perspective of occupational health medicine are discussed, and suggestions are made for future research.

Background

On the significance of the nose for the individual

"Sans nez, un homme
n'est plus un homme"
(In 'Le nez' by Nicolas Gogol)

The nose has a dual significance for the individual; it plays a key role in body image, and in the vital and relevant functions of breathing and smelling. Individuals have always been interested in the function and the role of the nose. Various illustrations of the body image and physiological role of the nose can be found in the world of arts and literature. The nose is the central character in the play *Cyrano de Bergerac* by Edmond Rostand; the children's novel *The adventures of Pinnochio* by Carlo Collodi; the story *Le nez d'un notaire* by Edmond About; the novel *The Nose* by Nicolai Gogol; and the bronze sculpture *Le Nez* by Alberto Giacometti, among others [1]. Similarly, the exciting function of the nose as source of the sense of smell is remarkably explored by Patrick Süskind in *Perfume* and Italo Calvino in *The Name, the Nose* [1]. French writer Marcel Proust also introduced the notion of "involuntary memory" in his famous series of novels *In Search of Lost Time* (À la recherché du temps perdu); this concept states that memory recall can occur in response to a specific smell.

Some characters in the above-mentioned literature had difficulties because of their noses. Similarly, it is difficult for many people to deal with an unattractive and/or functionally impaired nose. In such situations the individual's life may be disrupted to such an extent that which quality of life is affected [2]. As a consequence, subjects complaining of nasal symptoms and/or

body image are now sufficiently motivated to seek medical attention and/or undergo nasal surgical procedures.

The "united airways disease" concept

The respiratory system comprises of two functional compartments: the upper respiratory tract and the lower respiratory tract. The anatomical distinction between the two compartments has been artificially set at the level of the vocal cords.

The "united airways disease" (UAD) concept describes the relationship between the nose and lungs in the context of the expression of rhinitis and asthma. The model considers both disorders as two clinical manifestations of a single allergic disorder [3]. However, non-allergic mechanisms may also be considered in the model [4]. The evidence of the interaction between rhinitis and asthma is supported by observations made in epidemiology, physiopathology, and clinical medicine [3;5-7].

On the early recognition of the significance of the upper airways for the lower airways

The observation of a relationship between the nose and lungs is not a recent finding. It is mentioned several times in history. Early recognition of the importance of the nose and its interaction with the lower airways is found in a document from the first century AD by Galen entitled "On the usefulness of the parts of the body." Galen realized that inspired air does not pass directly into the lower airways but goes through the deflection of the inspired airflow into the nasal cavities; he suggested that this provides the lower airways with

some protection against noxious airborne agents, and conditions the inspired airflow that reaches the lungs.

"The beginning of the inspiration is not directly into the trachea, but there is a certain deflection of it..... which arrangement has a twofold advantage; first, because the air surrounding is at times quite cold and the lungs then would be chilled; and, secondly, because small particles of dust..... may not fall into the trachea"

"For I think this should be double advantageous: the parts of the lung will never be chilled when oftentimes the air surrounding us is very cold and the particles of dust, ashes or anything else of the sort frequently mixed with the air will not penetrate as far as the artery (trachea)"

Galen. On the usefulness of the parts of the body.
(Quoted from reference 9)

The observations made by Galen correspond in fact to the now-recognized main functions of the nose – i.e. the process of filtering, humidifying and warming approximately 10,000 to 20,000 litres of air passing through an adult nose each day.

Credit for the first description of hay fever or allergic rhinitis goes to John Bostock, a physician from London. In 1819, he published a report describing his own case; he had experienced regular and recurrent episodes of nasal and chest symptoms since he was eight years old [8].

"..... a general fullness is experienced in the head and particularly about the fore part; to this succeed irritation of the nose, producing sneezing, which occurs in fits of extreme violence, coming on at uncertain intervals. To the sneezings are added a further sensation of tightness of the chest, and a difficulty of breathing with a general irritation of the fauces and trachea. There is no absolute pain in any part of the chest, but a feeling of want of room to receive the air necessary for respiration, a huskiness of the voice, and an incapacity of speaking aloud for any time without inconvenience."

Bostock J. Case of a periodical affliction of the eyes and chest.
Med-Chir Trans 10: part 1:161-165, 1819.

Bostock's report may be not only the first description of allergic rhinitis, but also the first description of UAD, as the author's report describes the concomitant manifestation of asthma and rhinitis symptoms. Interestingly, Bostock also speculated on the effects of exposure in the causation of respiratory symptoms: "a bright glare of light, dust or some other substances touching the eyes, and any circumstance which increases temperature." [8] However, it was not Bostock who first demonstrated the causal association between nasal and chest symptoms and exposure to pollens. In 1873 in England, Charles Blackley, who also suffered from hay fever, published the results of experiments done on himself demonstrating that pollen caused hay fever [8]. Backley's experiments may be regarded as evidence of the first attempt to demonstrate a joint reaction of the nose and lungs by means of a challenge test, as he applied pollen to his nostrils and inhaled it to observe the appearance of nasal and chest symptoms.

Despite the fact that the coexistence of rhinitis and asthma in the general population has been anecdotally and empirically observed over the past two centuries, the perception of the upper and lower respiratory tract as two different compartments persisted until the last decade. The reasons for that split may be diverse but the link with advances in medicine cannot be ignored. The rapid development of modern medicine led to the establishment of two medical specialties - otorhinolaryngology and pneumology - that directed and promoted the growth of all areas of knowledge related to the upper and lower respiratory tract, respectively. This approach resulted in the rapid development of both medical specialties but also contributed to maintaining a misconception of the upper and lower respiratory tract as two independent

anatomical areas. Over the years, the investigation of the physiology, pathology, clinical manifestations and therapeutic features of diseases of the nose and lungs has been conducted relatively independently, as illustrated by a citation found in an otolaryngology textbook published in the 1980's. The author wrote: "My otolaryngological colleagues have commonly preferred to consider the respiratory tract as ending at the larynx; while my friends in respiratory physiology and disease equipped with nose clip and mouthpiece, have considered the nose itself a nuisance to be ignored, or at least avoided." [9] The author made this statement to stress the importance of avoiding rigid anatomical boundaries in the clinical practice of otolaryngologists and pneumologists and also to advocate the concept of the respiratory tract as a unit.

Although overall it has long been recognized that the nose plays an important role in protecting the lower airways, only recently the observation of the coexistence of rhinitis and asthma led to the formulation of the hypothesis that both conditions may be manifestations of a same allergic disease [10]. Over the last decade, the growing volume of scientific literature reporting findings from epidemiological and clinical studies demonstrating the close link between rhinitis and asthma has changed the perception of the respiratory tract as two different and functionally independent compartments [11]. Moreover, the current available knowledge of UAD has been translated into global health initiatives such as ARIA (Allergic Rhinitis and Its Impact on Asthma) launched by the World Health Organization, which recommended an

integrated diagnostic and therapeutic approach to the management of rhinitis and asthma [11].

On the contemporary observations of the link between rhinitis and asthma

Epidemiological observations in the general population

Epidemiological studies have shown that rhinitis and asthma frequently coexist; subjects with rhinitis are more at risk of developing asthma and rhinitis usually precedes asthma [12]. In the general population the prevalence of allergic rhinitis is approximately three times that of asthma [13]. Cross-sectional studies reveal that a high percentage of people suffering from asthma have rhinitis [10]. It has been estimated that up to 80 to 90% of patients with asthma report nasal symptoms and 20 to 50% of patients with allergic rhinitis report asthma symptoms [6].

A nested case-control study compared 173 incident patients with physician-confirmed asthma with 2177 subjects who reported no asthma symptoms; the analysis showed that subjects with rhinitis were three times more likely to develop adult-onset asthma [14]. In a 23-year longitudinal study [15] of college students, asthma developed in 10.5% of subjects with allergic rhinitis in compared to only 3.6% in subjects without this condition. A population-based study showed that asthma and bronchial hyperreactivity were more frequent in subjects with rhinitis than in those without (Odds Ratio: 6.63; 95% CI, 5.44 to 8.08; and Odds Ratio: 3.02; 95% CI, 2.66 to 3.43, respectively) [16]. A prospective population-based study demonstrated that allergic rhinitis was highly prevalent in subjects with allergic asthma; the results also supported the

appearance of allergic rhinitis preceding or developing concurrently with allergic asthma [17].

Epidemiological observations in the workplace

There are few epidemiological studies providing evidence on the interaction between rhinitis and asthma of occupational origin. Occupational rhinitis (OR) is reported to occur two to three times more frequently than occupational asthma (OA) [18]. An occupational survey conducted in Canada assessed the frequency of rhinitis symptoms among subjects with OA as well as the timing of occurrence of the symptoms in relation to asthma symptoms. Symptoms of rhinitis were reported by 92% of the subjects; and symptoms were more often reported as appearing before OA in the case of high molecular weight (HMW) agents [19]. Work-related rhinitis symptoms have also been reported as appearing before asthma symptoms in bakers [20], apprentice bakers [21], and hairdressers [22;23].

A multi-centre study of 212 subjects referred to four tertiary-care clinics for investigation of OA showed that nasal itching was a satisfactory predictor of OA objectively confirmed by specific inhalation challenge (SIC) particularly in subjects exposed to HMW agents [24]. A Finnish register-based study showed that patients with OA were older than patients with OR; authors suggest that this may be an indication that OR precedes OA [25]. Another Finnish study showed an increased risk of asthma (RR: 4.8, 95% CI 4.3 to 5.4) among subjects with OR compared to subjects with other occupational diseases [26]. The higher risk of asthma was observed for farmers, animal handlers and wood workers. With regard to low molecular weight (LMW) agents, there is

evidence from case-reports of a progression from rhinitis to OA in workers exposed to ninhydrin [27], isocyanates [28], and acrylates [29].

Pathophysiologic observations

Common histological features may facilitate a reaction of the respiratory tract as a unit in response to different offending exposures [3]. The lining of the nose and the bronchi consists of a ciliated pseudostratified columnar epithelium; the submucosa of both structures shows vessels, nerves, mucous glands, connective tissue and a similar profile of inflammatory cells. The nose plays an important role filtering out particles before they land on lower airways. Therefore, the nose is the organ in which immunological and nonimmunological responses may take place first after exposure to offending agents.

The exposure of the lower respiratory tract to poorly conditioned air may contribute to the malfunctioning of the lower airways. Experimental studies demonstrate a decrease in forced expiratory volume and an increase in nasal resistance in asthmatic subjects who are instructed to hyperventilate with cold air through the mouth [30]. Mouth breathing may result in worsening of exercise-induced bronchospasm [31]

Airway hyperresponsiveness is a characteristic feature of asthma that has also been observed in nonasthmatic subjects with rhinitis. An increased occurrence of bronchial hyperresponsiveness (BHR) and impairment in spirometric parameters has been documented in nonasthmatic patients with both seasonal and perennial allergic rhinitis in clinical studies [32;33]

During nasal challenge tests, it is possible to document an increase in BHR that suggests a common pathogenic mechanism for both the nose and the bronchi [34;35]. Nasal challenge with allergens conducted in subjects with allergic rhinitis can induce a bronchial response manifested by an increase in airway responsiveness, bronchoconstriction and influx of eosinophils [36;37]. Interestingly, performing a segmental bronchial challenge can induce an increase in eosinophils in both bronchial and nasal biopsies of rhinitic patients before and 24 hours after the challenge [38]. An experimental study showed that a similar degree of eosinophilic inflammation can be documented in nasal biopsies not only in asthmatic patients with nasal symptoms but also in asthmatic patients without clinical evidence of rhinitis [39]. Bronchial biopsies taken in asthmatic and rhinitic patients after challenge testing show the same morphologic characteristic in terms of cell influx and basement membrane thickening supporting the hypothesis of a common inflammatory reaction [40].

The existence of a systemic induction of inflammation would be another mechanism to link the nose and the bronchi; one study demonstrated an increase in the bone marrow production of precursors of eosinophils after intranasal allergen challenge [41].

During the performing of SIC with high-and-low molecular weight agents in subjects with confirmed OA it is possible to document nasal responses in regard to symptoms, nasal resistance and inflammatory cells and mediators that may help to characterize OR[42].

Clinical observations

In clinical practice the treatment of rhinitis has been observed to improve the control of asthma [43]. The most effective treatment for rhinitis and asthma is the use of topical corticosteroids. The use of intranasal corticosteroids to treat allergic rhinitis reduces bronchial hyperresponsiveness and asthma symptoms in asthmatic patients [44]. Antihistamine therapies have also shown beneficial effects in rhinitic patients with asthma reducing bronchial hyperresponsiveness and decreasing symptoms and the need for medication [45;46].

Novel therapies using leukotriene receptor antagonists also seem to be effective in improving asthma and rhinitis symptoms in subjects who suffer from both conditions [47]. Clinical trials have shown that anti-immunoglobulin E therapy with omalizumab improves quality of life and prevents asthma exacerbations in patients with concomitant asthma and allergic rhinitis [48].

The impact of rhinitis treatment on asthma severity has been assessed from a public-health perspective. Studies show that the proper management of allergic rhinitis has an effect on asthma morbidity by reducing hospitalizations and emergency-room visits by subjects with co-existent asthma [49-51].

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PART I

Joint investigation of occupational rhinitis and occupational asthma

Foreword to Part I

This section constitutes the main part of my research project. Chapter 1 addresses the link between rhinitis and asthma in an attempt to verify the concept of a "united airways disease" by using occupational rhinitis and occupational asthma as a model. To accomplish this task, I set up a clinical protocol, test-piloted it and carried out 18 months of patient investigations. I am presenting this work in the format of a manuscript already submitted for publication.

The main finding of this research was the demonstration of a concomitant reaction in the nose and bronchi in a group of study subjects after challenges with occupational agents. This finding constitutes additional objective evidence in support of the "united airways disease" concept and confirms its applicability to rhinitis and asthma of occupational origin.

CHAPTER ONE

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Occupational rhinitis in workers investigated for occupational asthma
Submitted

Abstract

Background. The links between asthma and rhinitis are nowadays referred to as the united airways disease (UAD). Current evidence shows that the UAD model seems to be applicable to occupational rhinitis (OR) and occupational asthma (OA).

Objective. We aimed to objectively assess, in the context of specific inhalation challenge (SIC) testing, the concomitance of bronchial and nasal reaction in the investigation of OA and OR

Methods. Forty-three subjects with a history of work-related asthma symptoms underwent SIC for confirmation of OA and investigation of OR. During SIC, subjects underwent assessment of changes in bronchial calibre by spirometry and assessment of nasal patency and nasal airway inflammation by acoustic rhinometry and nasal lavage.

Results. Twenty-nine SICs tested positive for OR and 18 SICs tested positive for OA. A joint diagnosis of OR and OA was made in 14 instances. This association was statistically significant (Prevalence rate ratio= 1.7; 95% CI=1.04 to 2.26) and more often observed in subjects challenged with high molecular weight (n= 12/27) than low-molecular weight agents (n= 2/23). Among subjects with OR, nasal lavage showed a significant increase in eosinophils at 30 min post-exposure that was still apparent 6 h later and correlated with changes in nasal patency.

Conclusion. This study provided objective evidence in support of the UAD concept by using OR and OA as a model for demonstrating the interaction between asthma and rhinitis. We demonstrated that OR can be assessed by

objective means; this condition frequently coexists with OA but can be present without OA.

Introduction

Occupational asthma (OA) is the most frequent work-related lung disease [1]. As the inflammatory process in the bronchi can also affect the upper airways, the study of occupational rhinitis (OR) in conjunction with OA is of interest. The link between rhinitis and asthma in the general population has led to the proposed 'united airways disease' (UAD) model, which also appears to be applicable to OR and OA. Rhinitis symptoms are common among subjects with OA [2]. However, evidence of the link between OR and OA is not as abundant or empirically described as the link between rhinitis and asthma in the general population.

The diagnosis of OA and OR is challenging because it entails the objective demonstration of significant changes in lung and nasal status after exposure to occupational agents in order to confirm the causal association between the occupational exposure and the disease. This diagnosis can be confirmed by performing specific inhalation challenges (SICs) in which the worker is exposed to the suspected agent [3]. This test is considered the "gold standard" for confirming OA. By contrast, there is no standardized procedure to confirm OR; however, assessment of changes in clinical and functional parameters by means of subjective and objective methods during nasal provocation test with suspected aetiological agents is thought to represent an ideal approach for confirming OR [4-7]. The use of objective means includes monitoring changes in nasal patency using acoustic rhinometry (AR) and/or rhinomanometry and the assessment of the secretory inflammatory reaction by nasal lavage (NAL) [6].

The aim of the present study was to objectively assess, in the context of specific inhalation challenge testing, the concomitance of bronchial and nasal reaction in the diagnosis of asthma and rhinitis following exposure to occupational agents. An ancillary objective was to assess nasal changes in cellular markers of inflammation after challenge.

Methods

Study subjects

The study population consisted of 43 subjects with a history suggestive of OA referred to the Hôpital du Sacré-Coeur de Montréal for SIC during the period from August 2005 to February 2007. Subjects were offered an evaluation of nasal responses during the SIC as an attempt to investigate OR. The evaluation of the nose was not offered if 1) subjects reported a history compatible with a recent common cold, rhinosinusitis or allergic rhinitis exacerbation; 2) subjects were on regular medications for nasal symptoms; 3) subjects had antecedents of recent nasal surgery; and 4) subjects had significant structural abnormalities such as nasal septum perforations or nasal polyposis based on anterior rhinoscopy examination carried out by an otolaryngologist. Ethical approval for the study was obtained from the Hospital Medical Ethics Committee and informed consent was obtained from each subject.

Design

Each SIC investigation involved evaluating a single agent during a control day and 2 to 4 active days depending on the time of occurrence of the asthmatic

reaction or when the maximum duration of exposure had been achieved in the absence of an asthmatic reaction. In most instances, subjects were assessed within the same week. Two challenge methodologies were used: 1) recreating working conditions in small cubicles or 2) with a closed-circuit apparatus that exposes subjects to lower and stable concentrations of the suspected occupational agent, or using both methodologies [8-10]. The rationale for selecting one method over the other as the initial procedure was the limited possibility of the closed-circuit equipment to generate the active or control agent.

The investigation of OA by SIC is a common and standardized procedure in our hospital [11]. On the first day the worker is exposed for 30 minutes to a control inert substance (i.e. lactose in the case of high-molecular-weight (HMW) agents, and a control chemical product (xylol) in the case of isocyanates and other low-molecular-weight (LMW) agents) in order to assess non-specific bronchial and nasal responses. The assessment of lung function involves monitoring forced expiratory volume in 1 second (FEV_1) before exposure and then every 10 minutes for one hour, every 30 minutes for two hours and then hourly for a total of 8 hours. In the case of HMW agents, exposure is carried out on a single day because these products cause immediate or dual reactions. For LMW agents, the exposure is progressively increased from day to day due to the possibility of late reactions that are difficult to predict [12]. The suspected offending agent is identified from a detailed occupational history, a review of the material safety data sheets and the results of specific skin prick tests in the case of HMW (proteinaceous)

agents. Bronchial responsiveness to methacholine and induced sputum examination are performed following standardized methodologies [13;14] at the end of the control day and at the end of the day on which a positive reaction is observed or when the total exposure time is reached.

Figure 1. The joint SIC protocol: joint assessment of nose and lungs

Time	Measurements	
	Nose	Lung
-20 min	AR, NAL	------
-10 min	------	FEV_1
0	challenge	challenge
+10 min	AR	FEV_1
+20 min	------	FEV_1
+30 min	AR, NAL	FEV_1
+40 min	------	FEV_1
+50 min	------	FEV_1
+60 min	AR	FEV_1
+90 min	-------	FEV_1
+120 min	AR	as before
+180 min	as before	⇩
+240 min	⇩	
+300 min		
+360 min	AR, NAL	
+420 min	AR	

AR, acoustic rhinometry; NAL, nasal lavage;
FEV_1, forced expiratory volume in 1 second

As shown in Figure 1, the assessment of nasal responses during SIC was carried out in parallel to the assessment of lung responses. This assessment continued until the day the exposure induced an asthmatic response or to the end of the maximum period of exposure (usually 120 min but occasionally -in two SICs- 240 min) despite the observation of a positive reaction in the nose before completing the evaluation of the lung. During each SIC session nasal responses were monitored by AR and nasal lavage (NAL). The monitoring consisted of a pre-challenge assessment and nine subsequent post-challenge

assessments. Upon arrival of the subject (at 7:30 a.m.) a baseline assessment is done after a 20-minute resting period. Then the subject is challenged with the suspected offending agent and after the total exposure time, measurements are performed at 10, 30 and 60 minutes and then each hour for the subsequent six hours. NAL is performed at baseline and at 30 minutes and six hours after the exposure.

Acoustic rhinometry

A trained technician performed AR according to a standardized procedure[15]. An acoustic rhinometer (Hoods Laboratories, Pembroke, Mass.) was used to measure the nasal volume between 2-5 cm into the nose (Vol_{2-5}) and the minimum cross-sectional area (MCA) and to compute the respective means. The Vol_{2-5} was selected as endpoint for this study to better reflect mucosal changes during the challenge [15]. AR is performed with the subject in a sitting position; temperature and humidity are monitored and kept constant during the day and the subject is instructed to avoid physical activity. With the subject in a sitting position and breathing quietly through the mouth, an appropriate nose adapter is selected, a lubricating jelly is applied on the adapter to create good coupling and sealing with the nostril, and AR parameters are measured. Three measurements with a coefficient of variation equal to or less than 6% are obtained for each nostril to calculate total Vol_{2-5} and total MCA.

Nasal lavage

The NAL protocol was adapted from the procedure described by Naclerio et al [16] and has been described in detail elsewhere [17]. Briefly, the subject is

instructed to avoid breathing and swallowing and say "K-K" repeatedly for 10 seconds in order to prevent the fluid being swallowed during the procedure by closing the velopharynx with this action. Then, 5cc of isotonic saline (0.9%) is instilled into one nostril. After 10 seconds the subject expels the fluid into a container; the procedure is performed in the other nostril and the sample is collected and pooled in the same container and immediately placed on ice. NAL samples are processed within 2 hours. The supernatant was obtained by centrifugation of the sample volume at 3300 rpm for 8 min at 4°C and then frozen at -80°C for future analysis. The pellet was re-suspended in 0.5 mL phosphate-buffered saline (PBS) containing 0.1% wt/vol bovine serum albumin. Cytocentrifuge preparations were made by using 100 microl of the remaining re-suspended cell suspension. The preparation was centrifuged at 450 rpm and slides were stained with Wright-Giemsa to perform differential cell counts. Slides were examined blindly. Leukocyte counts were expressed as a percentage of 300 cells counted and determined by means of light microscopy.

Complementary assessments

Study subjects completed a questionnaire that assessed the frequency of nasal symptoms and smoking habits. Atopy was assessed by skin prick test to a set of twenty allergen extracts; a subject was considered atopic if at least two allergens elicited a wheal at least 3mm in diameter with a negative control (glycerine, 50%) and a positive reaction to histamine phosphate.

Definition of outcomes

Changes in nasal airway patency and bronchial calibre constituted the main outcomes in this study. A decrease in $Vol_{2\text{-}5}$ of $\geq$ 30% after exposure was considered a positive diagnosis of OR in the absence of a positive reaction during the control day. Such a response was considered a sign of significant objective lower nasal airway patency for the analysis. The $\geq$ 30% threshold was selected from the analysis of the variability of the AR endpoint of all study subjects during their control sessions [18]. A decrease in FEV_1 of $\geq$ 20% after exposure was considered positive for the diagnosis of OA [19].

Statistical analysis

A contingency table was constructed to present the number of responders and non-responders to the bronchial and nasal challenges. The association between nasal and bronchial parameters was contrasted by chi-square and Fischer's exact test analysis. The strength of the association between nasal reaction and bronchial reaction was estimated by computing prevalence rate ratio and their 95% confidence intervals. Pearson and Spearman rank methods were used to perform correlations in parametric data and non-parametric data respectively. The Wilcoxon matched-pairs signed test was used to assess within subject changes in cell differentials in NAL between days of investigation. A 5% level of significance was applied to statistical analysis. Statistical analyses were performed by using SPSS 14.0 for Windows (SPSS, Inc., Chicago, Il).

Results

The initial study population consisted in 53 subjects in which 53 control sessions were conducted. Ten subjects were excluded from the study after their control session due to the observed fluctuations in AR measurements. A negative nasal reaction to the control substance was a pre-requisite to continue with the active challenge in the following days. A total of 50 SICs with high- and low- molecular weight agents performed in 43 subjects were analyzed. A subject might have two SICs with different agents.

Table 1. Baseline anthropometric and clinical characteristics of subjects

Characteristics	
Subjects n	43
Male: female	30 (70): 13 (30)
Age yrs	41.4 ± 10.1
Atopy positive:negative:unknown	32(74): 7 (16): 4 (9)
Smoking S:ES:NS	7 (17): 11(28): 22 (35)
Duration of exposure at work (yrs)	13.6 ± 11.2
Duration of work-related asthma symptoms (yrs)	4.94 ± 4.6
FEV_1 % predicted	97.8 ± 17.0
$PC_{20} \leq 16$ mg/ml (n/total, %)	26/43/60.4
Vol_{2-5}, cm^3	2.78 ± 0.8
MCA, cm^2	0.52 ± 0.1
Molecular weight of suspected agents high:low-molecular-weight agent	21 (49): 22 (51)
History of nasal symptoms * all: high: low-molecular-weight agent	
Runny nose	32 (80): 16 (89):16 (73)
Sneezing	33 (83): 16 (89): 17 (77)
Blocked nose	29 (73): 14 (78): 15 (68)
Itching	29 (73): 14 (78): 15 (68)

Data are presented as n (%) or mean ± SD
S: smoker; ES: ex-smoker; NS: non-smoker;
PC_{20}: concentration of methacholine that caused a 20% fall in FEV_1
* Number of subjects (%) reporting nasal symptoms in all subjects and based on molecular weight of suspected agent
Data on smoking habits and nasal symptoms was available from 40 subjects

Table 1 shows that the majority of subjects were atopic and non-smokers or ex-smokers. The mean duration of exposure to the suspected occupational agent was 13.6 years. Rhinitis symptoms were frequent in the study

population. The prevalence of each symptom of rhinitis was above 68%. However, no difference was observed in the prevalence of nasal symptoms based on a final positive or negative diagnosis of OA (data not shown). The prevalence of all nasal symptoms was higher in the group of workers exposed to HMW as compared to LMW agents (Table 1).

Acoustic rhinometry values

The analysis of data from all SIC showed that on the control day of exposure the mean ± SD (range) maximum percentage decreases in AR as compared to baseline were 13.2% ± 8.8% (0% to 28%) for $Vol_{2\text{-}5}$, and 11.9% ± 8.4% (0% to 30%) for MCA. On challenge days of exposure to the active agents, the mean maximum percentage decreases were 31.8% ± 16.5% (0% to 81%) for $Vol_{2\text{-}5}$ and 25.6% ± 16.5% (0% to 77%) for MCA. The correlation between $Vol_{2\text{-}5}$ and MCA measuring these changes during the control day ($r = 0.56$; $p < 0.01$) and challenge day ($r = 0.88$; $p < 0.01$) was satisfactory and significant.

Results of bronchial and nasal response to the challenge

Table 2 shows the outcome of the 50 SICs included in the analysis. Among those with significant changes in bronchial calibre, most (14/18) also had significant low nasal airway patency. Among those with no significant low bronchial calibre, about half had significant low nasal airway patency (15/32).

Table 2. Outcome of SICs based on nasal and bronchial response and type of suspected agent

Group	All SICs			HMW			LMW		
	Low bronchial calibre*			Low bronchial calibre*			Low bronchial calibre*		
Low nasal patency [§]	Yes	No	Total	Yes	No	Total	Yes	No	Total
Yes	14	15	29	12	5	17	2	10	12
No	4	17	21	4	6	10	0	11	11
Total	18	32	50	16	11	27	2	21	23
PRR (95% CI)	**1.7 (1.04, 2.26)**			**1.7 (0.9, 3.1)**			**2.10 (0.7, 2.1)**		
p-value	0.04[&]			0.2[β]			0.5[β]		

*Clinically significant: decrease in FEV1 ≥ 20% from baseline after challenge
[§] Clinically significant: decrease in Vol2-5 ≥ 30% from baseline after challenge
PRR, prevalence rate ratio; [&] in chi-square test; [β] in Fischer's exact test

Twenty-nine of 50 SICs (58%) were positive for OR and 18 of 50 SICs (36%) were positive for OA. A joint diagnosis of OR and OA was made in 14 instances. The prevalence rate ratio (PRR) expressing the association between the diagnosis of OR and OA (significant low bronchial calibre and nasal congestion) was 1.7 (95% CI=1.04 to 2.26). An example of an SIC positive for both OR and OA is shown in Figure 2.

The causal agents tested in the fourteen SICs that were classified as positive for both OA and OR in Table 2 comprised HMW (flour = 9; animal allergens= 2; guar gum = 1) and LMW (isocyanates =1; polyvinyl resin = 1) agents.

Table 2 also shows that among subjects who reacted to HMW agents, there were 17 diagnoses of OR and among subjects exposed to LMW agents there were 12 diagnoses of OR. In 12 instances there was a diagnosis of both OR and OA in the group challenged with HMW agents. The PRR expressing the

association between the diagnosis of OR and OA in this group was 1.7 (95% CI= 0.9 to 3.1). A joint diagnosis of OR and OA was observed in only two instances in the LMW group.

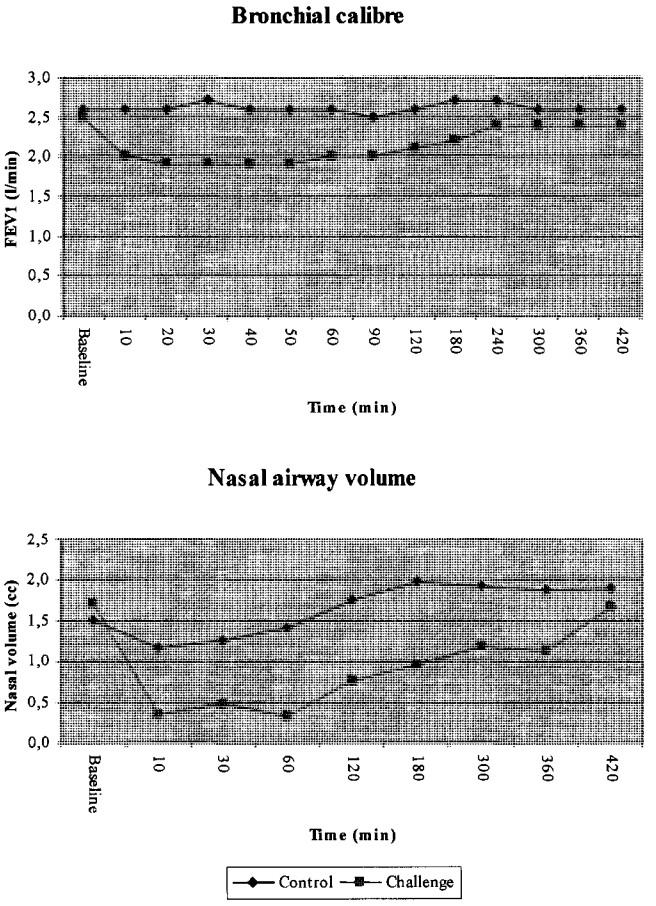

Figure 2. Example of SIC (control and active challenge day) positive for OR and OA due to a HMW agent (animal allergen). Time marks indicate baseline (pre-challenge) and post-challenge nasal and bronchial measurements in the same session. The threshold for a positive reaction in the bronchi and nose was reached at 10min post-challenge. The maximum fall in FEV1 and nasal volume from baseline values during the active challenge day was 27.5% at 30min and 81.0% at 60min respectively.

Bronchial hyperresponsivenes at baseline ($PC_{20} \leq 16$ mg/ml) was detected in 60.3% of the study subjects (Table 1). Bronchial hyperresponsiveness at baseline was found to be associated to a final diagnosis of OA after SIC (p= 0.01). This association was also observed among subjects with a final

diagnosis of OR alone (p= 0.06) or of both OA and OR (p= 0.08). Results showed no association between atopy status and a final diagnosis of OR alone, OA alone or both diagnosis in the same subject (data not shown)

Results of nasal lavages

NAL samples from twenty-five SICs were analysed. NAL was not performed in all SICs due to unavailability of the technique (15 cases); subjects refused the test (5 cases) or were not able to follow the instructions to collect the sample (5 cases).

The analysis of NAL performed in 25 SICs (HMW= 14, LMW=11) showed that the predominant types of cells at baseline on the control and active day were neutrophils and epithelial cells. There were no statistically significant differences in the percentage of neutrophils, macrophages and epithelial cells comparing the control and active day (data not shown). Lymphocytes were not analyzed because the samples demonstrating these cells were few and the number of cells was too low.

Table 3 shows that provocation with the control agent did not induce significant changes in the percentage of eosinophils on the control day in subjects diagnosed or not with OR. By contrast, provocation with the active agent resulted in an increase in the percentage of eosinophils in the group of subjects with OR at 30 min and 6 hours after total exposure in comparison to baseline values; the early eosinophilic response was statistically significant (p= 0.01).

Table 3. Changes in percentage of eosinophils in NAL after exposure to control and active agent during SIC

Subject group			Challenge time		
	n	Agent	Before	30 min	6 h
OR (+)	15	control	0.90 ± 1.9	0.93 ± 2.2	0.81 ± 1.6
	15	active	0.93 ± 2.2	4.05 ± 7.6	2.22 ± 5.0
		p-value	0.2	0.02	0.1
OR (-)	8	control	0.66 ± 0.6	0.66 ±1.2	0.16 ± 0.2
	9	active	0.06 ± 0.1	0.96 ± 1.6	0.81 ± 2.0
		p-value	na	0.6	0.4

Numbers represent mean percentage and standard deviation
OR(+), positive diagnosis for occupational rhinitis by acoustic rhinometry
OR (-), negative diagnosis for occupational rhinitis by acoustic rhinometry
p-value compares the percentage of eosinophils between the control and active day
n, number of SIC

Comparison of the nasal early reaction (at 30 min after exposure) on the control and active day demonstrated a statistically significant difference in the percentage of eosinophils in the group of subjects diagnosed with OR (0.9% vs 4.0%). The difference in eosinophilic response between the control and active day was still apparent at 6 hours post exposure (0.8% vs 2.2%) but without reaching statistical significance (Table 3). There were no significant differences in the early and late eosinophilic response in the group of subjects who did not have OR.

Figure 3 illustrates the association between NAL and AR parameters. After SIC, there was a satisfactory and significant correlation between the percentage increase in eosinophils measured in NAL at 30 min post-exposure and the maximum percentage decrease in nasal volume measured by AR ($r= 0.528$, $p= 0.007$)

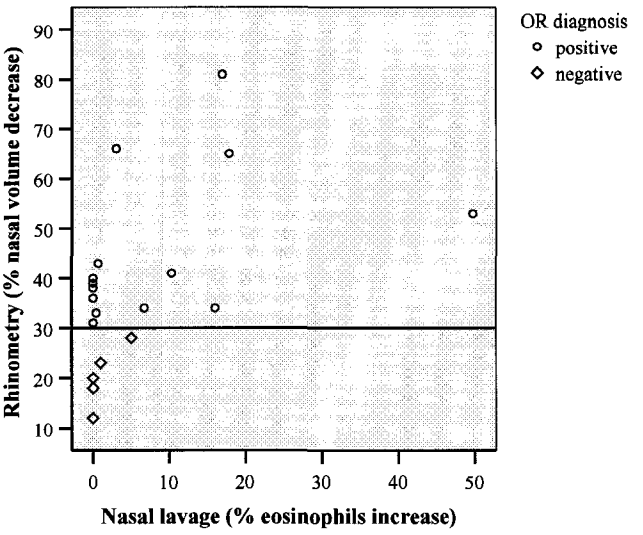

Figure 3. Relationship between changes in nasal patency and eosinophil counts during SIC. The reference line indicates the threshold for a positive diagnosis of OR with acoustic rhinometry

Discussion

Results of this study with subjects referred for investigation of possible OA showed that: 1) OR can be assessed by objective means; 2) OR frequently coexists with OA and can be present without OA. The results demonstrated the applicability of the UAD concept to work-related asthma and rhinitis. They also provide further objective evidence in support of the UAD concept by using OA and OR as a model to demonstrate the interaction between the upper and lower airways.

Our subjects comprised a selected population of workers with a history of asthma symptoms in which a high frequency of nasal symptoms was seen. The prevalence of symptoms -runny nose, sneezing, nasal blockage and itching- was 80%, 83%, 73% and 73%, respectively (Table 1). After carrying out SIC

using AR to monitor changes in nasal patency, we found that a confirmed diagnosis of OR was more frequent (29/50; 58.0 %) than a confirmed diagnosis of OA (18/50; 36.0 %). These results stress the importance of using objective means in the investigation of OR in order to gain a more accurate perspective of the impact of this disease. They also point out the relevance of using means to also assess upper airways in the context of the assessment of OA.

The association between rhinitis and asthma in the general population has been demonstrated in epidemiological studies. Rhinitis may be present in up to 80% of patients with asthma [20]. In our study, the association between OR and OA followed the same pattern, with OR occurring in 77.8% (14/18) of confirmed cases of OA (Table 2).

Our study demonstrated an overall concomitant significant decline in nasal patency and bronchial calibre in 14 of 50 SICs (28.0 %) and a concomitant absence of a response in 17/50 SICs (34.0 %); therefore, agreement on the outcome of the diagnostic investigation was present for 62.0% of investigations (31/50) (Table 2). These changes allowed us to make an objective diagnosis of OR and OA in the same patient, supporting the applicability of the UAD model to rhinitis and asthma of occupational origin. The evidence of UAD in this study relies on assessing the major physio-pathologic changes involved in rhinitis and asthma, i.e. obstruction of the upper airways assessed by reduction in nasal volume, and obstruction of the lower airways assessed by changes in bronchial calibre. We confirmed a clinically significant "united airways" response that was statistically

significant (PRR: 1.7; 95% CI= 1.04 to 2.26). This "united response" was more apparent in the case of HMW than LMW agents (12/27, 44.4 % versus 2/23, 8.7 %) and almost statistically significant in the case of HMW agents (PRR: 1.7; 95% CI= 0.9 to 3.1) (Table 2). The results suggest that this configured occupational UAD is more clearly defined in those cases due to agents known to induce an allergic IgE-mediated immunological response. Among subjects with no significant decrease in bronchial calibre, about half (15/32; 46.8%) had significant lower nasal airway patency. This means that when there is significant lower nasal airway patency, there is not necessarily any change in lower airways calibre. Accordingly, the results showed that in 15 SICs a diagnosis of OA was not made and therefore OR was the sole diagnosis. This situation is independent of the type of causal agent (HMW or LMW).

A "stepwise sensitization" may occur where the nose, as first line of defence against noxious substances, becomes sensitized first and then the sensitization process progresses down the respiratory tract through the pharynx and larynx until it reaches the bronchi. According to this pattern, we would expect a gradual worsening of lower respiratory tract symptoms among those subjects with OR alone that may ultimately lead to a clear manifested OA if exposure to the offending agent continues. Thus, occupational UAD would only be present in advanced cases, those whose bronchi have become sensitized, this association being more likely in our study that included workers symptomatic of OA for the relatively long interval of 4.9 ± 4.6 years. The comparison of the number of years with OA symptoms based on a final diagnosis after SIC of OR alone or a joint diagnosis of OA and OR showed that the period was

longer among those finally classified as having both OA and OR (7.4 ± 5.0) compared to those with OR alone (5.7 ± 4.9).

In our study we did not observe any significant nasal reaction in 4 of 18 SICs (22.2%) positive for OA in which, based on the UAD model, we would expect a reaction in both the nose and the bronchi. Two instances may be explained by the induction of an immediate bronchial reaction (at 20 sec and 7 min after the start of the challenge) that precluded extended exposure. Although plausible it seems unlikely; we do not know if the carry-over of the exposure might have induced a significant reaction in the nose because in all cases positive for both OR and OA, the nose reacted always before the bronchi. The explanation for the other two cases is yet to be determined.

Analogous to induced sputum examination in the investigation of OA, [21] performing NAL may have an additional diagnostic value in the investigation of OR. Our results confirm findings from previous studies that showed that challenges with HMW and LMW agents can induce an influx of eosinophils that can be demonstrated in NAL samples [22-24]. We observed an increase in the percentage of eosinophils ≥ 3% in 8 NAL samples (HMW= 5; LMW= 3); five of these samples corresponded to cases positive for both OR and OA after SIC. Our study clearly showed a significant increase in the percentage of eosinophils at 30 min post-exposure in comparison to baseline values on the active day and also when comparing the percentage of eosinophils on the control and active day at the same time after the challenge in the group of subjects with a confirmed diagnosis of OR alone. This increase was still

apparent 6 hours after exposure and was significantly correlated with the observed changes in nasal patency measured by AR (Figure 3). In line with other studies [23], we noticed no significant increase in the proportion of neutrophils after the challenge with either the control or active agent. Based on our findings the assessment of upper airways inflammation by the NAL technique and the assessment of nasal patency by AR are complementary and therefore can be recommended for the investigation of OR. However, AR appears to be more easily applicable and feasible than the NAL technique.

Further research efforts in the investigation of OR in the context of the UAD model should focus on determining the pathogenic mechanisms involved in the expression of OR alone or in association with OA for the two categories of causal agent (HMW and LMW). Tests to characterize induced inflammation in the upper and lower airways and their association after exposure to HMW and LMW agents should also be carried out in a larger population.

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PART II

Methodological considerations of main investigative methods

Foreword to Part II

Reproducibility is a crucial characteristic in the context of specific inhalation challenge for the accurate assessment of changes resulting from the test. The validity of results presented in Part I of this thesis depends on the accuracy of the investigative methods used to diagnose occupational rhinitis. The utilization of objective methods allows for more accurate diagnosis of occupational rhinitis. In occupational health medicine this is imperative because labelling a disease as occupational entails legal implications. For this reason, the investigation of occupational rhinitis in our study was performed with objective means, i.e, acoustic rhinometry and nasal lavage. Chapter 2 and Chapter 3 of this part of the thesis present two studies we conducted to assess the reproducibility of acoustic rhinometry and nasal lavage respectively, in order to assess their applicability and feasibility in the setting of respiratory challenges with occupational agents. The reproducibility of these tests had never previously been examined in this context. Our results showed that both methods were sufficiently reproducible to be included in our protocol investigating occupational rhinitis.

CHAPTER TWO

Castano R, Theriault G, Gautrin D, Ghezzo H, Trudeau C, Malo JL

Reproducibility of acoustic rhinometry in the investigation of occupational rhinitis
Am J of Rhinol. 2007; 21(4): 474-477

Abstract

Background. To diagnose occupational rhinitis, it is mandatory to conduct an objective assessment of changes in nasal patency during specific inhalation challenge (SIC). The reproducibility of acoustic rhinometry measurements in the setting of occupational challenges has never been examined.

Objective. This study assessed the reproducibility of acoustic rhinometry during SIC investigation of occupational rhinitis.

Methods. Twenty-four subjects underwent acoustic rhinometry measurements during SIC investigation of occupational rhinitis. Subjects attended 3 to 6 days of SIC within a week by means of a realistic or closed-circuit apparatus methodology

Results. All the within-day intraclass correlation coefficients (ICCs) for nasal volume (2-5 cm) and minimum cross-sectional area (MCA) based on a different number of measurements (2 to 7) were above 0.85; all the coefficients of variation (CVs) for the same parameters were low (below 10%). The between-day CVs based on different numbers of SIC sessions ranged from 8.0% to 8.8% and from 6.8% to 8.8% for nasal volume and MCA, respectively. The between-day ICCs ranged from 0.80 to 0.88 and from 0.83 to 0.94 for nasal volume and MCA, respectively.

Conclusion. Acoustic rhinometry showed good within- and between-day reproducibility and can be recommended for the objective monitoring of nasal patency during SIC investigating occupational rhinitis.

Introduction

Occupational rhinitis is a clinical entity of growing importance and interest that may affect a significant number of workers in occupations at risk, but for which estimates of prevalence and incidence vary, due in part to different diagnostic criteria (1). For the diagnosis of this condition, it is mandatory to confirm that the nasal obstruction is work-related (2). To achieve this, the subjective sensation of nasal patency reported by a patient needs to be assessed by subjective and objective measurements. The use of objective measurements minimizes misclassification of the disease and improves diagnostic accuracy. The monitoring of changes in nasal patency during nasal provocation tests using objective measurements is currently the recommended approach to the diagnosis of occupational rhinitis (3).

Acoustic rhinometry is a technique that assesses nasal patency objectively by determining the intranasal volume between selected segments and the cross-sectional area of the nasal cavity (4;5). The validity of acoustic rhinometry assessed by different methodologies is now fully recognized (6;7). Features of acoustic rhinometry, such as its rapidity and the limited need for patient cooperation, make it particularly promising for nasal challenges in which repeated measurements are necessary to demonstrate changes in nasal patency following occupational exposures. In such settings the reproducibility of the technique is crucial to the accurate monitoring of changes in nasal airways.

Although the use of acoustic rhinometry has increased in the past decade in clinical practice and research, no studies have assessed the reproducibility

of acoustic rhinometry in the clinical setting of inhalation challenges for the investigation of occupational rhinitis. This paper examines the within- and between-day reproducibility of acoustic rhinometry for the monitoring of changes in nasal patency during specific inhalation challenge (SIC) in the investigation of occupational rhinitis.

Methods

Study subjects

We analyzed data from 24 subjects (19 men and 5 women), aged 26-65, with a history suggestive of occupational asthma who had been referred to the Hôpital du Sacré-Coeur de Montréal for SIC. An evaluation of nasal responses was conducted during the SIC as an attempt to investigate occupational rhinitis. The evaluation of the nose was not offered if 1) subjects reported a history compatible with a recent common cold, rhinosinusitis or allergic rhinitis exacerbation; 2) subjects were on medications for nasal symptoms; 3) subjects had antecedents of recent nasal surgery; and 4) subjects had significant structural abnormalities found by anterior rhinoscopy, such as nasal septum perforations or evidence of nasal polyposis. Participation was voluntary. Ethical approval of this study was obtained from the Hospital Medical Ethics Committee and informed consent was obtained from all subjects.

Acoustic rhinometry

A trained technician performed the acoustic rhinometry according to a standardized procedure (8). An acoustic rhinometer (Hoods Laboratories,

Pembroke, Mass.) was used to measure the total volume between 2-5 cm (Vol2-5) into the nasal cavity and the minimum cross-sectional area (MCA) and to compute the respective means. In our laboratory, acoustic rhinometry is performed after an acclimatization period of 20 minutes with the subject in a sitting position; the temperature and humidity are kept constant during the day and the subject is instructed to avoid physical activity. With the subject in a sitting position and breathing quietly through the mouth, an appropriate nose adapter is selected, lubricating jelly is applied on the adapter to create good coupling and sealing with the nostril, and measurements are taken. Three measurements with a CV equal to or less than 6% are obtained for each nostril to calculate the total Vol2-5 and the total MCA.

Design

Each subject attended 3 to 6 days of SIC. In most instances, subjects were assessed within the same week by means of a realistic (n=17) or closed-circuit apparatus (n=7) methodology (9). Subjects are assessed by the realistic methodology when the suspected agent is not suitable to be administered by means of the particles or vapours generator (closed-circuit apparatus methodology). Subjects with antecedents of seasonal allergic rhinitis were studied out of their allergy seasons. Briefly, on the first day the subject is exposed to a control inert substance in order to assess nonspecific nasal responses. This is considered the control day. On the following days, the subject is gradually challenged with the suspected offending agent for up to 2 to 4 hours or until the exposure induces an asthmatic response or to the end of the maximum period of exposure. The suspected offending agent is

determined from a detailed occupational history, the revision of material safety data sheets of products to which the worker is exposed to and skin prick testing in those cases in which a high molecular weight agent is the suspected agent. The monitoring of nasal responses with acoustic rhinometry during the SIC consists of a baseline measurement (pre-challenge) and 8 subsequent measurements (post-challenge). The subject arrives early each morning and a baseline measurement is taken. Then the subject is challenged with the suspected offending agent and after the total exposure time, measurements are taken at 15, 30 and 60 minutes and then each hour for the next 6 hours.
For each participant, the within-day measurements taken on the control day were used to assess the within-day reproducibility of the acoustic rhinometry. The between-day reproducibility analysis includes the pre-challenge measurement from the control day, the pre-challenge measurements from sessions in which no positive response was observed and the pre-challenge measurement from the session in which a positive response was observed. The threshold value for a positive response was a 25% decrease in nasal volume measured with acoustic rhinometry in the SIC.

Statistical analysis

The within- and between-day reproducibility of acoustic rhinometry parameters (Vol2-5, MCA) was expressed as: (a) intraclass correlation coefficient (ICC). For interpretation, good reproducibility was defined as an ICC greater than 0.8 (10); (b) coefficient of variation; and (c) coefficient of repeatability; a representative example of good reproducibility is shown graphically (Figure 1) presenting the limits of agreement (mean difference ±2

SD) by the Bland and Altman method (11). Differences in the reproducibility of acoustic rhinometry measurements based on the methodology used to conduct the SIC (realistic versus close-circuit apparatus) were analyzed with the t-test for unpaired data. Data were analyzed using the statistical package SPSS 14.0 for Windows.

Results

Within-day reproducibility

Table 1 shows the within-day reproducibility of the acoustic rhinometry parameters (Vol2-5, MCA). All the ICCs calculated for Vol2-5 and MCA based on different numbers of measurements taken during the day showed values above 0.85.

Table 1. Within-day reproducibility of acoustic rhinometry during SIC

		Vol2-5		MCA	
n	N	CV	ICC and 95% CI	CV	ICC and 95% CI
22	7	9.2%	0.86 (0.77-0.93)	9.2%	0.93 (0.88-0.96)
22	6	8.4%	0.90 (0.82-0.95)	8.7%	0.94 (0.89-0.97)
24	5	8.3%	0.89 (0.82-0.95)	8.5%	0.93 (0.88-0.96)
24	4	8.1%	0.90 (0.82-0.95)	8.2%	0.93 (0.88-0.97)
24	3	8.1%	0.90 (0.80-0.95)	8.2%	0.94 (0.88-0.97)
24	2	8.3%	0.88 (0.74-0.95)	7.4%	0.92 (0.82-0.97)

n, number of subjects; N, number of measurements; Vol 2-5, total nasal volume between 2 and 5 cm into the nose; MCA, minimum cross-sectional area; CV, coefficient of variation; ICC, intraclass correlation coefficient

Moreover, all the CVs calculated for Vol2-5 and MCA reflecting a different number of measurements taken during the day were low (below 10%)

Between-day reproducibility

Results shown in Table 2 report on the between-day reproducibility in the short term. The CVs for Vol2-5 and MCA reflecting a different number of sessions ranged from 8.0% to 8.8% and from 6.8% to 8.8%, respectively. The ICCs ranged from 0.80 to 0.88 for Vol2-5 and from 0.83 to 0.94 for MCA.

Table 2. Between-day reproducibility of acoustic rhinometry during SIC

		Vol2-5		MCA	
n	N	CV	ICC and 95% CI	CV	ICC and 95% CI
24	2	8.8%	0.84 (0.67-0.92)	6.8%	0.94 (0.86-0.97)
18	3	8.2%	0.80 (0.62-0.91)	8.1%	0.83 (0.68-0.93)
12	4	8.0%	0.88 (0.74-0.95)	8.8%	0.84 (0.66-0.94)

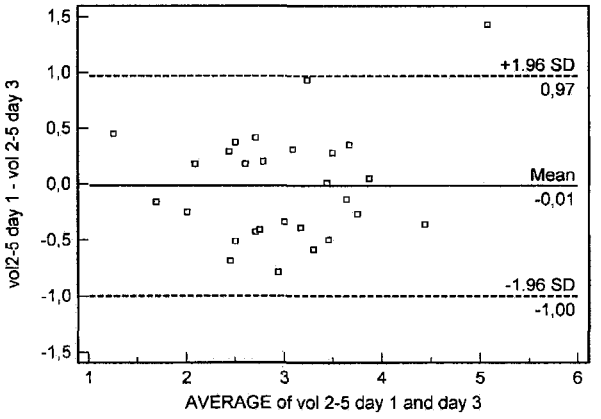
n, number of subjects; N, number of sessions; Vol2-5, total nasal volume between 2 and 5 cm into the nose;MCA, minimum cross-sectional area; CV, coefficient of variation; ICC, intraclass correlation coefficient

An assessment of reproducibility during a longer period was conducted in two subjects attending 8 sessions within a 4-week and 8-week period respectively. The ICC for Vol2-5 and MCA including only the measurement of the first and last session was 0.97. The ICC calculated for the measurements of the eight sessions was 0.94 in these two subjects.

Coefficient of repeatability

The between-day reproducibility is also illustrated by the coefficient of repeatability (CR) assessing the variation between the control day and one "active" SIC day. Figure 1 shows that the group mean difference was close to zero and that the lower and upper limits of agreement for 2 sessions (Day 1 and Day 3) were -1.00 and 0.97 respectively.

Figure 1. Bland-Altman plots of variability of acoustic rhinometry (Vol2-5) data during SIC. The mean Vol2-5 of each subject is plotted against the differences between Day 1 and Day 3. The limits of agreement (CR) are represented by the dotted lines (±2 SD).



Discussion

The reproducibility of a method is often assessed in healthy subjects to minimize individual variability. As shown in Table 3, acoustic rhinometry has demonstrated good reproducibility in experimental studies. Our study reports on the reproducibility of acoustic rhinometry in a larger population and in a clinical setting. This is the first study assessing the reproducibility of acoustic rhinometry in the context of SIC for investigation of occupational rhinitis. A few studies have examined the reproducibility of acoustic rhinometry in other nasal challenge settings (Table 3). Overall, the CV was lower in experimental studies than in studies comprising a nasal challenge. This may be explained by factors such as the exposure itself occurring during the SIC, special training of subjects, and also the fact that in most experimental studies 12,14,15,16 a decongestant was used before the measurements to reduce the effect of the physiological congestion induced by the nasal cycle.

Table 3. Studies assessing the reproducibility of acoustic rhinometry

Author, year	N	Subjects status	Setting	Volume outcome	Between-day CV		Within-day CV	
					VOL	MCA	VOL	MCA
Silkoff PE, 1999 [12]	6	Normal	experimental	0-5 cm	5.2%	8.9%		
Roithmann R, 1995 [13]	14	Normal	experimental	0-8 cm	4.0%	5.0%	9.0%	10.0%
Grymer LF, 1991 [14]	24	Normal	experimental		4.0%			
Sipila J, 1996 [15]	9	Normal	experimental	2-7 cm	16.4%			
Fouke JM, 1992 [16]	8	Normal	experimental	0-10 cm			7.9%	
Kesavanathan J, 1996 [17]	29	Normal	challenge *		20.0%	26.0%	16.0%	23.0%
Larivee Y, 2001 [18]	20	Normal (10) Rhinitics (10)	challenge**		7.3% (N) 8.6% (R)			
This study	24	Asthmatics Rhinitics	challenge***	2-5 cm	8.2%	8.1%	9.2%	9.2%

N, number of study subjects; CV, coefficient of variation; VOL, nasal volume; MCA, minimum cross-sectional area; (N), normals; (R), rhinitics

* Subjects challenged with clean air and smoke

** Subjects challenged with saline phosphate and histamine

*** Subjects challenged with occupational agents. Results presented are from 18 subjects during 3 sessions (between-day) and from 22 subjects during 1 session (within-day)

Our results show that acoustic rhinometry is a method with good within- and between-day reproducibility. As shown in Table 1 and 2, all the within- and between-day CVs were below 10% and all the within- and between-day ICCs were above 0.80. These results are comparable to those reported by Larivee et al. (18) and better than those observed by Kesavanathan and Swift (17) (Table 3). We did not observe a fall in reproducibility over time. Between-day reproducibility was good analysing data from either 2 sessions (ICC, 0.84) or 4 sessions (ICC, 0.88). These results support the use of acoustic rhinometry during SIC with consecutive sessions within one week, as was the case in this study. Perhaps the shorter interval of time between sessions was the reason why our study showed better reproducibility than that reported by Kesavanathan and Swift,(17) in which subjects were challenged at weekly intervals over one month. The results of this study also showed no significant

difference in within-day reproducibility (p= 0.6, unpaired t-test) and between-day reproducibility (p= 0.6, unpaired t-test) when comparing the type of methodology used to conduct the SIC (realistic versus closed-circuit apparatus).

Results shown in Table 1 from data obtained during the control day support the use of the technique on the same day. Generally, no exaggerated responses are expected during the control day and the observed variations in nasal parameters may be attributed to the anticipated normal physiological fluctuations of the nasal cycle. Despite exposure to a nonspecific control substance, our subjects did not experience greater variations in their measurements during the control day, which is relevant considering that this should be a prerequisite to exposure to the potentially "active" occupational agent, i.e., the one suspected of causing occupational rhinitis.

In this study we observed good between-day reproducibility. This is an essential condition in the context of nasal challenges. The fact that subjects were exposed to an agent for different periods and that this could have created a carryover effect affecting the baseline measurements might be considered a limitation of the study. Results show that this did not happen and despite the fact that most challenge sessions were conducted on consecutive days, the interval between sessions was long enough to return to baseline conditions at the start of the next session.

In conclusion, this study showed that acoustic rhinometry is a reproducible technique that can be recommended for the objective monitoring of changes in nasal patency during SIC investigation of occupational rhinitis.

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CHAPTER THREE

Castano R, Theriault G, Maghni K, Ghezzo H, Malo JL, Gautrin D

Reproducibility of nasal lavage in the context of the inhalation challenge investigation of occupational rhinitis
Am J of Rhinology. In press

Abstract

Background. The nasal lavage (NAL) method is increasingly used to assess changes in upper airways inflammation in the investigation of occupational rhinitis (OR). A good reproducibility of the method is fundamental to accurately assess changes in markers of inflammation in nasal secretions before and after inhalation challenges.

Objective. The main objective of this study was to assess the short-term reproducibility of cells and cellular markers of inflammation in NAL in the setting of specific inhalation challenge (SIC) investigating OR. An ancillary objective was to assess the reproducibility of NAL in the context of two different SIC methodologies.

Methods. Twenty-five subjects attended the laboratory for two separate days of NAL performed within the same week. On the first visit subjects underwent NAL before a SIC sham session and on the second visit before a SIC with the active agent. These pre-challenge NAL measurements obtained on both days were used to analyse the reproducibility of the NAL method.

Results. The reproducibility for cell differential counts was satisfactory: for neutrophils, (ICC=0.68); for eosinophils, (ICC=0.95); for macrophages, (ICC=0.77); and for epithelial cells (ICC=0.73). The reproducibility of total cell counting was poor (ICC= 0.12). The reproducibility of eosinophil cationic protein (ECP) concentrations was satisfactory (ICC= 0.67). Eosinophils counts were reproducible in the context of two different challenge methodologies.

Conclusion. The NAL technique demonstrated to be sufficiently reproducible to be considered useful for the monitoring of upper airways inflammation during the investigation of OR by SIC.

Introduction

The assessment of the inflammatory status of the upper airways is of rising interest in respiratory research. Means such as biopsy and cytology have been used to characterize the cellular and humoral response of the nasal mucosa to environmental and occupational agents [1-3]. These methods assess directly normal and inflammatory events but their invasive character restricts their systematic use in clinical practice and in research. Sampling nasal secretions offers an alternative objective means to assess upper airways inflammation.

Analogously to the utilization of induced sputum for the assessment of lower airway inflammation in the investigation of occupational asthma (OA), the nasal lavage (NAL) method has been used to investigate occupational rhinitis (OR) in epidemiological and experimental studies [4-6]. Because of inter-individual variability, studies in which subjects serve as their own control are more suitable for assessing the reproducibility of NAL [7]. As such, specific inhalation challenges (SIC) used to diagnose OA and OR offer a good research set up. In the SIC investigation of OR subjects are challenged during a control and active challenge days either by recreating working exposure conditions within a small challenge room (the realistic method) or by means of a generator of particles and aerosols (the closed-circuit method). The latter methodology delivers during the challenge low and stable concentrations of the suspected agent which, in theory, cause less irritation to the respiratory tract as compared to the 'realistic method' [8;9]. Physiological changes in the nose resulting from the controlled exposition to the agent are monitored before and after the challenge. The monitoring of upper airways inflammation by

sampling and analysing nasal secretions is a relevant parameter to be considered in OR investigation protocols. However, the selected method must be sufficiently reliable to monitor changes in airways inflammation in order to be included in such a protocol.

The main objective of this study was to assess the short-term reproducibility of NAL measurements of total cell count, cells differentials and eosinophilic cationic protein (ECP) values in the context of SIC. We also wanted to evaluate the reproducibility of NAL measurements in the context of two different SIC methodologies (realistic and closed-circuit methods).

Methods

Subjects and Protocol

We analyzed data from 25 subjects (17 men and 8 women), aged 26-58 with a history suggestive of OA referred to the Hôpital du Sacré-Coeur de Montréal for SIC during the period from August 2005 to February 2007. A parallel assessment of nasal responses that included the performing of NAL was offered to these subjects. The evaluation of the nose was not offered if 1) subjects reported a history compatible with recent common cold, rhinosinusitis or allergic rhinitis exacerbation; 2) subjects were on medications for nasal symptoms; 3) subjects had antecedents of recent nasal surgery and 4) subjects had significant structural abnormalities such as nasal septum perforations and nasal polyposis. Subjects with antecedents of seasonal allergic rhinitis were studied outside their allergy seasons.

It was not the objective of this study to assess the reproducibility of a nasal challenge test monitored by NAL but to assess the reproducibility of two

baseline NAL measurements in the context of our SIC protocol investigating OR. Thus, study subjects underwent NAL on two separate days of SIC within the same week. NAL was performed before the start of each SIC session. The NAL was performed at the same time of the day (8:00 am) after a 20 minutes resting period. In each SIC session subjects are challenged with a control agent on the first visit and with the suspected occupational agent on the next visit. The NAL was performed before each challenge to avoid the effect of the exposure on the measurements and therefore to achieve physiological conditions as stable as possible for the assessment of the reproducibility of the measurements on the two visits. With this approach the measurement in the first visit was not influenced by any exposure and the measurement in the second visit might have some influence only from the exposure on the control day. Usually, we observe no clinically significant reaction after the exposure to the control agent, however if such an influence was likely it may be evidenced in the reproducibility of the two measurements.

Study subjects were challenged during the control day by means of the closed-circuit method (n=15) or the realistic method (n=10). The outcome measurements included the total and differential cell count and concentrations of ECP. Approval for this study was obtained from the Hospital Medical Ethics Committee and informed consent was obtained from all subjects. Participation was voluntary.

Nasal lavage technique and processing

The NAL technique used in this study was adapted from the procedure described by Naclerio et al [10]. With the subject in a sitting position with the

head flexed 45° backwards 5 ml of pre-warmed at 37°C isotonic saline (0.9%) is instilled into one nostril. Previously, the subject was instructed to avoid breathing and swallowing and say "k-k" repeatedly for 10 seconds in order to prevent the fluid being swallowed during the procedure by closing the velopharynx. After 10 seconds the subject expels the fluid into a plastic container previously stored in a refrigerator. This is followed by a NAL performed in the other nostril. The sample is collected and pooled in the same container and placed immediately on ice. Within 2 hours the NAL sample was processed. Sample volume was measured and the total cell count was calculated in a hemocytometer. The supernatant was obtained by centrifugation of the sample volume at 3300 rpm for 8 min at 4°C and then kept frozen at -80°C until analysis. The pellet was re-suspended in 0.5 µl PBS containing 0.1% (wt/vol) bovine serum albumin fraction. Cytocentrifuge preparations were made by using 100 microl of the remaining re-suspended cell suspension. The preparation was centrifuged at 450 rpm and slides were stained with Wright-Giemsa to perform differential cell counts. Slides were examined blindly. Leukocyte counts were expressed as a percentage of 300 cells counted and determined by means of light microscopy. Nasal fluid samples were concentrated by centrifugation on Centricon centrifugal filter device YM-3 (Millipore; FisherScientific, Montreal, PQ, Canada) with a 3,000 molecular weight cutoff as previously described [11]. ECP levels in NAL concentrated samples were measured using a commercially available Elisa Kit (MBL Co., LTD., Nagoya, Japan) following the manufacturer's instructions. Optical densities were determined using the ELISA reader Elx 808iu (Bio-Tek Instruments, Inc., Richmond, VA), and calculations were performed using the

KC4 software (Bio-Tek Instruments, Inc.). Data were adjusted for the factor of concentration and expressed as ng/ml [11].

Statistical analysis

Reproducibility of NAL measurements was determined for sample volume, total cell counting (TCC), neutrophils, eosinophils, macrophages, epithelial cells, and ECP; lymphocytes were not analysed because the samples demonstrating these cells were few and the numbers of cells were too low. Reproducibility was expressed by computing intraclass correlation coefficient (ICC) and graphically represented by the Bland-Altman plots [12] for two visits (MedCalc statistical software, Mariakerke, Belgium). Significance was accepted at 95% level. Differences in the percentage of cells between visits were compared by the Wilcoxon rank sign test and a 5% level of significance was applied. Data was analyzed using the statistical package SPSS 14.0 for Windows.

Results

Overall the technique employed to perform the NAL was well accepted by subjects. Four subjects discontinued the evaluation after the first NAL because they were not able to follow the instructions or they considered the procedure uncomfortable.

Table 1. Reproducibility of NAL measurements during SIC (n= 25 pairs)

Variable	Visit 1	Visit 2	ICC
Volume, cc	5.4 ± 1.7	5.9 ± 1.1	0.53
TCC, 10^6/ ml	0.06 ± 0.09	0.04 ± 0.08	0.12
Neutrophils, %	41.2 ± 37.5	45.8 ± 35.2	0.68
Eosinophils, %	0.7 ± 1.6	0.7 ± 1.9	0.95
Macrophages, %	6.7 ± 6.9	8.1 ± 8.6	0.77
Epithelial cells, %	51.4 ± 35.6	43.9 ± 35.1	0.73
ECP, ng/ml*	1.3 ± 1.8	0.9 ± 0.8	0.67

TCC, total cell counting; ICC, intraclass correlation coefficient; ECP, eosinophil cationic protein.
Numbers for visits represent mean and standard deviation
* sample size for ECP was 10 pairs and measurements were taken within 48 hours.

Data on cell differentials were available for 25 pairs. Data on ECP measurements were available for 10 pairs. Reproducibility of NAL cellular and humoral markers of inflammation is shown in Table 1. The analysis did not show differences statistically significant in the percentage of cells between visits. The reproducibility for all type of cells was satisfactory. The reproducibility of TCC was poor (ICC= 0.12). The reproducibility of ECP concentrations was satisfactory (ICC= 0.67). Figure 1 summarizes the reproducibility of cells percentages in the two visits.

Table 2 shows the reproducibility of cells components according to the type of SIC methodology used on the first visit in which subjects were challenged with a control agent. There were no differences in the percentage of cells between visits with both methods. Eosinophils counts were reproducible with both methods but slightly better with the close-circuit method (ICC= 0.96 versus ICC= 0.91). The reproducibility of neutrophils (ICC= 0.75) and epithelial cells (ICC = 0.83) was satisfactory with the closed-circuit method

Table 2. Reproducibility of cells in NAL based on type of challenge method

SIC method	Neutrophils	Eosinophils	Macrophages	Epithelial Cells
Generator*				
(n= 15)				
Visit 1	44.8 ± 42.1	0.7 ± 1.9	4.0 ± 3.9	50.4 ± 41.2
Visit 2	48.5 ± 39.5	0.6 ± 2.1	4.2 ± 3.2	44.4 ± 40.8
ICC	0.75	0.96	0.28	0.83
Difference p-value	0.5	0.6	0.7	0.5
Realistic §				
(n= 10)				
Visit 1	35.7 ± 30.5	0.8 ± 1.1	10.6 ± 8.6	52.9 ± 27.3
Visit 2	41.8 ± 29.1	0.7 ± 1.5	14.0 ± 10.7	43.3 ± 26.2
ICC	0.48	0.91	0.78	0.38
Difference p-value	0.6	0.7	0.1	0.3

SIC, specific inhalation challenge; ICC, intraclass correlation coefficient
* Closed-circuit method (particles and aerosols generator)
§ Realistic method (recreating working conditions)
p-value represents differences between the two visits in Wilcoxon test
Numbers for visits represent mean and standard deviation

and higher as compared to the 'realistic method'. Macrophages counts showed good reproducibility with the 'realistic method' and poor with the closed-circuit method.

Discussion

Methods to sample nasal secretions for the assessment of upper airways inflammation include absorption techniques (e.g, filter papers, foams), suction techniques and dilution techniques (e.g, NAL, nasal pool, Foley catheter) [13]. The selection of the technique should be based on its validity and reproducibility and also on the characteristics and objectives of the study in which it is applied. In our study we adapted the NAL method described by Naclerio et al [10] because it is simple and rapid to perform and it has a good

validity. These features were central in the context of our study that required repeated measurements of bronchial and nasal physiological parameters in the

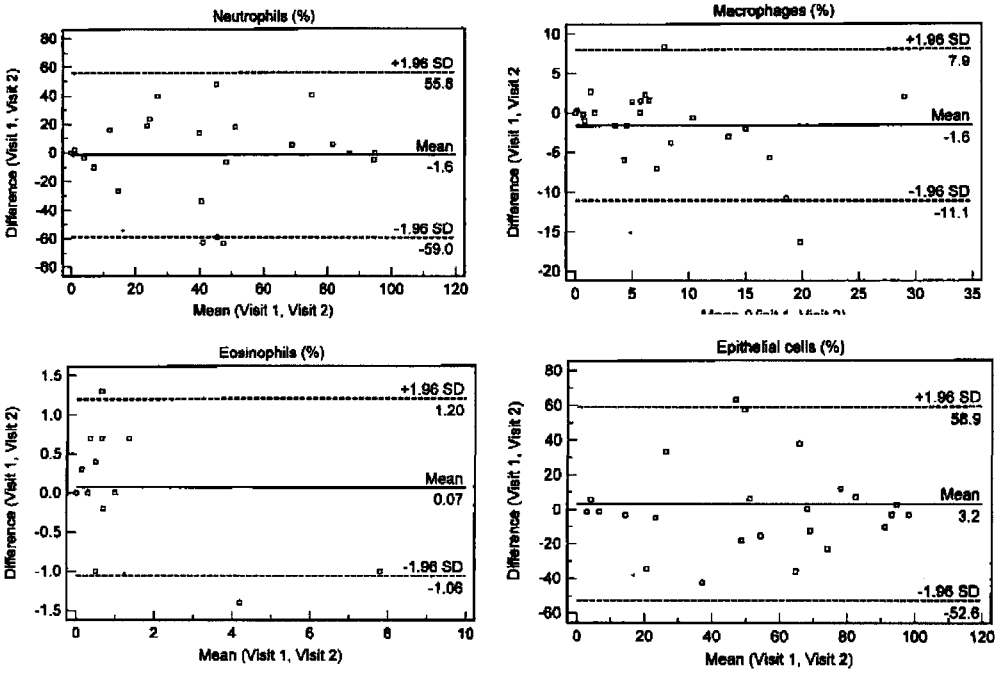

Figure 1. Bland-Altman summaries for the reproducibility of cells percentage in 25 pairs of NAL samples measured on two different visits. It is expected that 95% of the differences between measurements fall within 2 standard deviations of the overall average difference. The plots indicate satisfactory reproducibility since most individual values are scattered around the mean difference and lie within the limits of agreement.

same patient during SIC. Also, we wanted to use a technique in which it was less likely to provoke a physiologic response in the nose since nasal patency was also simultaneously monitored by acoustic rhinometry during the SIC.

The Naclerio technique is generally reported as well tolerable but requires good collaboration from the patient. The technique causes some discomfort during the instillation of the saline solution into the nose and subjects have difficulties to retain the fluid and to prevent swallowing it. Most articles describing this technique indicate that the patient should be instructed to close

the soft palate during the procedure to avoid swallowing the fluid but without a clear indication of the method to achieve this. Our technique in which subjects repeat continuously the letter 'k' during the NAL to close the velopharynx was found satisfactory. It was inspired by the Proetz method [14] used in otolaryngological practice to irrigate the paranasal sinus. With this technique the mean recovery of fluid in each visit was about 60% (Table 1). Most importantly, it was found comfortable by most subjects; a practical advantage is that it is easily explained to and understandable by the patient.

In spite of its extensive use in research studies the reproducibility of NAL by the Naclerio method has seldom been examined. Using this technique Belda et al [15] assessed the reproducibility of cells and ECP concentrations in healthy and rhinitic subjects on two visits separated by 48 hours. Among subjects with rhinitis the reproducibility was good for neutrophils (ICC= 0.7), eosinophils (ICC= 0.9), macrophages (ICC= 0.6) and epithelial cells (ICC= 0.8). They observed a poor reproducibility for cell differential counts in normal subjects. The reproducibility was also poor for TCC and ECP concentrations in both healthy and rhinitic subjects. In agreement with Belda et al. [15] we observed that cells differential are reproducible in two consecutive visits within one week (average within 3 days) (Table 1). We also observed that TCC has a poor reproducibility (ICC= 0.12) which may have an explanation in the range of variation of the sample volume between two visits; this NAL parameter is expressed per volume unit. According to this, TCC should not be considered as outcome to monitor changes during SIC. In contrast to the study by Belda et al.[15], we observed that ECP measurements

taken within 48 h were reproducible (ICC= 0.7) by the Naclerio method. Such a divergence is difficult to explain but some reasons may be found in methodological aspects regarding the study design and the processing of the NAL samples. Our study subjects were referred for SIC. The performing of SIC in our hospital is a standardized procedure in which the subject must attend 2 to 4 SIC sessions. NAL are performed at the same time of the day and subjects spend most of the day in the laboratory under well-controlled conditions. Thus, it is less likely that in the interval of time between visits the subject is exposed to environmental factors that may influence the outcome measurements in the second visit. Although the processing of the samples was similar in many aspects in both studies, we did not use dithiothreitol (DTT) in the NAL protocol to disperse cells. The use of DTT in the processing of induced sputum samples has been questioned on the basis of potential adverse effects on inflammatory mediators [16]. The effect of DTT in NAL samples has never been examined. However, Belda et al [15] observed a better reproducibility in their ECP measurements (ICC= 0.6) using a different technique of NAL sampling in which a higher volume of fluid is instilled and remains for a longer time in contact with the nasal mucosa.

The analysis of NAL based on the methodology used to carried out the SIC after the NAL on the first visit demonstrated that except for macrophage counts the reproducibility with the closed-circuit method was better than with the 'realistic method'. The closed-circuit method was developed in our hospital so as to challenge subjects with low, stable and well-controlled levels of occupational agents [8;9]. The exposure is better controlled than with the realistic approach where concentrations may at times be higher than the

Threshold Limit Value, Short Term Exposure Limit (TLV-STEL). Based on our findings these controlled exposure conditions seem to provoke a more controlled inflammatory response in the nose reflected in a good reproducibility of cells in NAL samples. In spite of the fact that study subjects were exposed to a non-specific agent during the control day and that the NAL were performed in most cases on consecutive days, there was not a residual or carryover effect influencing the NAL measurement on the second visit. The interval of time between both NAL was therefore long enough to return to return to pre-challenge baseline conditions.

A cutoff value that can be used to define a significant change in eosinophils counts in NAL after exposure to occupational agents has not been established. We found only one study [17] that proposed a 5% increase in eosinophils as the criteria to define a nasal provocation test as positive in subjects exposed to high molecular weight agents. Based on the reproducibility in eosinophils counts observed in our study, it seems that a 4% increase in eosinophils after nasal provocation may be an adequate cutoff point to classify a NAL test as positive if a cutoff value is set at 2 SD above the mean percentage change in eosinophils shown in Table 1.

In summary, in this study we observed that the reproducibility of cellular and soluble inflammatory markers of NAL samples on 2 separate occasions within 1 week was sufficiently reproducible to recommend this method in the assessment of upper airways inflammation in the investigation of OR by SIC. Changes in eosinophils > 4% after SIC can be considered as significant. More

studies should be conducted in a larger population on the reproducibility of cellular components in NAL with different sampling techniques and also addressing specifically the determination of a significant nasal reaction during challenge with NAL.

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PART III

Management considerations

Foreword to Part III

Despite current knowledge of the link between rhinitis and asthma, the management of both respiratory conditions - understood as diagnosis, treatment and prevention - continues in most cases to be conducted independently by otorhinolaryngologists and pneumologists. The following chapter presents a paper in the format of a Letter to the Editor that makes some reflections and suggestions on the need to formulate guidelines for the united management of patients suffering from rhinitis, asthma or both conditions considering the concept of a "united airways disease."

CHAPTER FOUR

Castano R, Malo JL

Towards a united management of united airways disease: the role of otorhinolaryngologists and pneumologists
Allergy 2007 Jun; 62(6): 708

Dear Editor:

The article by Civelek et al. entitled "Turkish physicians' perception of allergic rhinitis and its impact on asthma" (1) provides evidence of the necessity to continue developing a practical integrated approach to the management of patients suffering from rhinitis, asthma or both diseases. There seems to be sufficient awareness among physicians of the link between rhinitis and asthma but some difficulties arise when the time comes to implement recommendations suggested by guidelines such as those derived from the Allergic Rhinitis and Its Impact on Asthma (ARIA) initiative (2) .

The recognition by otorhinolaryngologists and pneumologists of the importance of regarding the respiratory tract as a whole becomes fundamental for the management of the "united airways disease". To start with, they should avoid setting rigid boundaries to the anatomical level of interest in their clinical practice. Overall, the diagnosis and treatment of rhinitis and asthma continue to be conducted independently by otorhinolaryngologists and pneumologists. Published articles have commented on the therapeutic implications of the "united airways disease," emphasizing the potential advantages of a judicious and well planned management of rhinitis and asthma based on evidence on the synergistic effects of drugs used in the treatment of both diseases (3,4,5). The ARIA initiative recommends an integrated diagnostic and therapeutic approach to the management of rhinitis and asthma. However, precise guidelines are necessary to achieve the ARIA recommendations. Both otorhinolaringologists and pneumologists are well aware of how to diagnose and treat patients suffering from rhinitis and asthma, respectively. However, it is important to formulate directives on the way they

should proceed for a "united" diagnostic and therapeutic approach to patients suffering from rhinitis, asthma or both diseases. It would be important to define (a) the respective roles of the otorhinolaryngologist, pneumologist and also the general practitioner, occupational health medicine specialist and allergy specialist; and (b) how to make a joint decision on the best management of the patient. Once all those involved in the management of rhinitis and asthma become aware of their role, it will be easier to formulate practice parameters at the different levels of health care. Ultimately, the results of an optimal "united" management of rhinitis and asthma will, we hope, translate into a better quality of life for those suffering from "united airways disease".

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PART IV

Nosological considerations

Foreword to Part IV

Occupational rhinitis is a relatively new domain in respiratory research. The reason for the increasing interest in this condition from the scientific community is its close link with occupational asthma. The availability of appropriate definition and classification is fundamental to understanding a disease and promoting research on that disease, as well as making it possible to compare results between studies. So far, no operational by consensus definition and classification of occupational rhinitis has been formulated as they exist for occupational asthma. The next three chapters address nosological aspects of occupational rhinitis proposing a new definition and classification of this disease.

CHAPTER FIVE

Castano R, Theriault G, Gautrin D

The definition of rhinitis and occupational rhinitis needs to be revisited
Acta Otolaryngol. 2006 Oct; 126 (10): 1118-9

To the Editor:

The recent paper by Storaas et al entitled "Occupational rhinitis: diagnostic criteria, relation to lower airway symptoms and IgE sensitization in bakery workers" (1) opens up an opportunity to stress the current lack of an accurate and standardized definition of occupational rhinitis. We agree with Storaas on the need for a consensus on diagnostic criteria for occupational rhinitis. However, we prefer to think in terms of a consensus definition of occupational rhinitis rather than on consensus diagnostic criteria that may vary with different type of occupational rhinitis.

In our opinion, the current definitions of occupational rhinitis as they exist in the literature do not reflect the complete dimension of the disease. Occupational rhinitis is the type of rhinitis that originates from exposures at the workplace; consequently, its definition should rely on a current accepted definition of rhinitis in general. However, the definition of rhinitis in the general population lacks accuracy as well. The most commonly cited and accepted definition of rhinitis is that formulated by the International Consensus Report (ICR) of 1994 stating that "rhinitis is defined as inflammation of the lining of the nose, characterized by one or more of the following symptoms: nasal congestion, rhinorrhea, sneezing and itching" (2). This definition is based on the description of symptoms secondary to an inflammatory reaction of the nasal mucosa. Therefore, any of the above nasal symptoms have the same weight in defining rhinitis. For example, a patient complaining of only itching will have a rhinitis. There is no scientific evidence to support such an example. Moreover, it is well established that nasal

symptoms such as nasal obstruction, nasal discharge, sneezing and itching alone or in combination may accompany nasal disorders that are not rhinitis.

As discussed by Storaas the ICR formulates another definition of rhinitis in an algorithm that they propose for the management of rhinitis (2). This alternative definition, that in fact conflicts somewhat with the one mentioned above states that rhinitis may be defined as the presence of "two or more symptoms for more than 1 hour on most days". This definition also has limitations because it does not state if it refers to any combination of nasal symptoms or if there are some symptoms in particular that should be taken into account at the time of defining rhinitis. In addition, the definition itself is not supported by published research studies.

These conflicting statements on the definition of rhinitis have important consequences for clinical practice and epidemiological research. In clinical practice it may create confusion on the diagnosis and the management of rhinitis. In epidemiological research such a definition leads to problems when assessing and comparing measures of disease frequency such as the prevalence of rhinitis between studies. The paper by Wang et al (3) cited by Storaas addresses in particular the problem of assessing the prevalence of rhinitis with different diagnostic criteria based on symptoms. This epidemiological cross-sectional study investigated the prevalence of rhinitis in Singapore using self-reported presence of one, two, three or four symptoms on most days during the past year as criteria to define rhinitis. The study showed that prevalence rates of rhinitis go from 25.5% to, 13.1% to, 6.5%, and to 3.0% respectively for the different number of symptoms. These results illustrate the variability of the

prevalence rate of rhinitis in the absence of a standardized definition of the disease.

A recent study also provides elements to support a reevaluation of the existing definitions of rhinitis. Ng et al (4) examined the relative importance of commonly reported symptoms, signs and diagnostic tests in order to define allergic rhinitis. A statistical ranking of variables according to prevalence, chi-square and strength of association (∂ value) showed that nasal symptoms were the most important criteria to define allergic rhinitis as compared to ocular and pharyngeal symptoms and to clinical signs and diagnostic tests. In the context of this discussion an interesting finding was that the ranking of symptoms from most to least important in allergic rhinitis showed runny nose and sneezing ranking first followed by sniffing and impaired sense of smell which are not considered common symptoms of rhinitis. Stuffed and itchy nose ranked below sniffing and impaired olfaction.

Taking into account the above considerations we consider that the revision of the definition of occupational rhinitis should start with the revision of the definition of rhinitis in general.

Occupational rhinitis is one type of rhinitis and, as discussed, results from epidemiological studies support the suggestion that a definition of rhinitis based only on the presence of symptoms may be imprecise and needs to be revisited. However, reaching a consensus on a definition of either rhinitis or occupational rhinitis that would meet the needs of both clinical practice and epidemiological studies may be difficult considering that there may be degrees of certainty to attribute a diagnosis depending on the availability of diagnostic tests. Moreover, in epidemiological studies, more likely to be based on self-

reported symptoms obtained by questionnaires, researchers use different definitions of rhinitis and/or occupational rhinitis depending on the purpose of the study.

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CHAPTER SIX

Castano R, Theriault G

Defining and classifying occupational rhinitis
J Laryngol Otol. 2006; 120 (10): 812-7

Abstract

Three categories of rhinitis may occur in the workplace: occupational rhinitis, work-aggravated rhinitis and rhinitis-like conditions. In the present paper, we propose a new definition and a new classification of occupational rhinitis that takes into account mechanisms of induction as well as its clinical presentation. In a parallelism with occupational asthma, occupational rhinitis is defined as a type of rhinitis characterized by intermittent or sometimes permanent nasal airflow limitation due to causes and conditions attributable to the work environment. According to mechanism of induction, occupational rhinitis is classified as immunological and irritant-induced (non-immunological) rhinitis. Occupational rhinitis of the immunological type can itself be episodic or persistent whereas the non-immunological type is subdivided into acute, chronic and corrosive

Introduction

Rhinitis and asthma are relatively common conditions in the general population but rhinitis is far more frequent than asthma (1, 2). Today, occupational asthma is the most prevalent respiratory occupational disease in developed countries (3). It is likely that occupational rhinitis is more prevalent than occupational asthma among work exposed populations. However, occupational rhinitis is much less known than occupational asthma. Contrary to asthma there is no standardized approach to diagnose occupational rhinitis; several determinants of occupational rhinitis such as incidence, prevalence, natural history and pathogenic mechanisms are not well understood and the morbidity burden of rhinitis of occupational origin on the worker and its family remains elusive. No definition and classification of occupational rhinitis has been discussed in depth in the specialized scientific literature. A standardized and by consensus definition and classification of occupational rhinitis is needed to better manage this entity and to compare research results between studies.

Defining occupational rhinitis

Defining a disease like occupational rhinitis constitutes a challenge. In so doing various approaches could be considered such as defining the disease in terms of histopathological, physiological or clinical characteristics either alone or in combination. As an example, a simple approach to the definition of occupational rhinitis would be to base it on both its main pathological feature that is "an inflammation of the mucous membrane lining of the nose" and its clinical manifestations (e.g, nasal obstruction, nasal discharge, sneezing), all

the above in the context of an occupational setting. However, this approach has limitations. As has been shown in recent studies on the remodeling of the upper airways in allergic rhinitis, the pathologic involvement observed in this disorder comprises not only the well established inflammatory infiltration but it also involves structural changes of the glands, the mesenchyma and even the vasculature of the nose (4). Therefore, a definition that refers only to "an inflammation of the mucosa" would be both incomplete and inaccurate.

The inclusion of clinical manifestations in the definition of occupational rhinitis is not exempt of difficulties either. Referring to common nasal symptoms does not reflect the specificity of occupational rhinitis. There are other nasal symptoms apart from runny nose, sneezing, nasal congestion that may manifest in workers exposed to allergens and irritants at the workplace. For example, formation of crusts is reported by Brisman et al in bakers exposed to flour (5) and dryness of the nose is reported by Kraus et al among workers exposed to cellulose contaning dust in the soft tissue paper producing industry (6). It is also well known that workers exposed to chromium in the electroplating industry suffer from frequent formation of crusts as a manifestation of more severe nasal manifestations such as nasal septal ulcerations and nasal septal perforations (7, 8). This approach can lead to difficulties in selecting those symptoms that should be included in the definition. To illustrate this aspect, Ng et al (9) study is quite revealing. They examined the relative importance of different recognized symptoms, signs and diagnostic tests as a base to the definition of allergic rhinitis in a group of 47 subjects with diagnosis of allergic rhinitis and 23 healthy subjects. The study showed that the ranking of symptoms from most to least important in allergic

rhinitis are runny nose and sneezing ranking first followed by sniffing and impaired sense of smell which are not traditionally grouped under the so called "common symptoms" of rhinitis. Furthermore, the other two commonly cited nasal symptoms namely, blocked and itchy nose ranked below sniffing and impaired olfaction. This observation confirms that a definition of rhinitis based on the presence of clinical symptoms alone may not be adequate

Taking into account the above considerations, a definition of occupational rhinitis modeled on the definition of occupational asthma which has wide acceptance may be more appropriate. Occupational asthma has been defined as "a disease characterized by variable airflow limitation and/or bronchial hyperresponsiveness due to causes and conditions attributable to a particular environment and not to stimuli encountered outside the workplace" (3). Notice that this definition is based on the presence of observable physiopathological changes that occur in the lower airways. Occupational rhinitis may be defined as a *type of rhinitis characterized by intermittent and sometimes permanent nasal airflow limitation due to causes and conditions attributable to the work environment*. Like the definition of occupational asthma, this definition of occupational rhinitis is based on a physiopathologic finding namely, the demonstration of variable or permanent nasal airway limitation and its necessary work-relatedness.

Although similar, this definition of rhinitis has two important differences with the definition of occupational asthma. The first is the temporal clinical presentation of occupational rhinitis. In contrast to occupational asthma in which the patient may be asymptomatic from one episode to another, symptoms of rhinitis are not infrequently continuous with the affected victim

complaining permanently. Secondly, a physiopathological manifestation resembling bronchial hyperresponsiveness is not taken into account in the above definition of occupational rhinitis. Increased airway responsiveness to nonspecific stimulus is a characteristic of asthma which can be objectively provoked by the administration of increasing concentration of histamine or methacoline causing a decrease in FEV1 by 20% from the baseline value (10). Nasal hyperreactivity may be analogous to bronchial hyperresponsiveness, namely an exaggerated response of the nose to nonspecific stimuli eliciting nasal airway narrowing. Unfortunately, in spite of several attempts, no investigative method has been found that would trigger a nasal hyperreaction in a way similar to the provocation tests used to trigger a bronchial hyperreaction in an asthmatic patient (11).

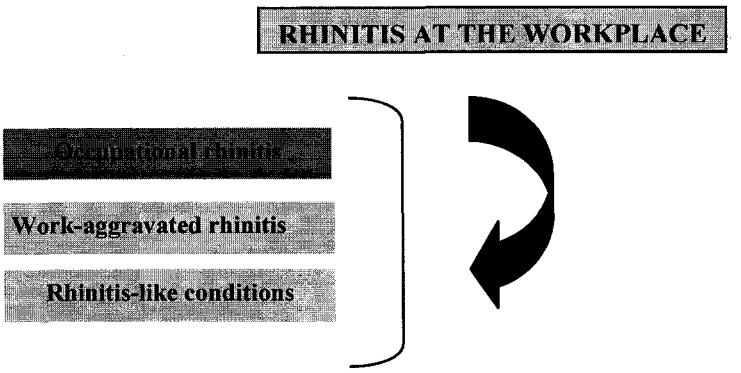
We believe that for the purpose of defining rhinitis of occupational origin it is fundamental to consider a physiological change in the nose that may be attributed to the work environment and that at the same time is measurable by objectives techniques. Nasal obstruction meets this criterion. It can be evaluated by clinical examination and be demonstrated objectively by methods such as acoustic rhinometry, rhinomanometry and peak nasal inspiratory and expiratory flow techniques. Furthermore, the rationale to consider nasal obstruction in any definition of rhinitis and of course in those cases of rhinitis of occupational origin secondary to either allergens or irritants exposures is that it is the nasal symptom that best reflects the underlying pathological mechanism involved namely, inflammation of the nasal mucous membrane. The hypothesis in this case is simple; any degree of inflammation of the nasal

mucosa should in theory lead to a decrease in nasal patency that may be objectively measured.

A new classification of rhinitis at the workplace

An approach similar to the well known and accepted classification of asthma observed at the workplace (12) is proposed here to classify rhinitis of occupational origin in a way that might be useful for clinical practice and epidemiologic research. As shown in Fig 1, we distinguish three categories of rhinitis that may occur in the workplace: occupational rhinitis, work-aggravated rhinitis and rhinitis-like conditions. Rhinitis may either be caused or exacerbated by exposure at the work environment. Rhinitis caused by an occupational exposure meets the definition of occupational rhinitis. Subjects with work-aggravated rhinitis are people with a pre-existing rhinitis in which symptoms are triggered by exposures to irritants at the workplace such as fumes, vapours, and dusts. The category "work-aggravated rhinitis" is borrowed from the concept of work-aggravated asthma which comprises a pre-existing asthma aggravated by a workplace exposure (12).

Figure 1. Types of rhinitis at the workplace



Contrary to asthma, there are no studies supporting the existence of work-aggravated rhinitis. Nevertheless, there are reasons to believe that it is not erroneous to utilize this term when classifying rhinitis at the workplace. First, rhinitis is three times more prevalent than asthma in the general population (11). As a consequence, many people with actual rhinitis do enter the workforce. They might be exposed to occupational irritants and/or allergens that will exacerbate or worsen their preexisting rhinitis. Second, empirical knowledge derived from otorhinolaryngological practice indicates that this category is indeed highly likely. It is common among otorhinolaryngologists to assess patients with the diagnosis of rhinitis (others than occupational) who claim that their symptoms are made worse by exposures at work. We therefore propose that work-aggravated rhinitis becomes a formal category within the class of rhinitis at the workplace.

Rhinitis-like conditions refer to certain specific exposures at work that may generate rhinorrhea that mimics rhinitis. It is the case for exposures to cholinesterase-inhibiting substances such as organophosphates pesticides, and to cold air. Organophospates (e.g, carbaryl, malathion, parathion, pyrethrum) are rapidly absorbed after inhalation. They increase the activity of the secretory glands that induce an intense watery nasal discharge. Cold air exposure is associated with increased rhinorrhea due to enhanced glandular secretory activity in which cholinergically-mediated neuronal pathways are involved (13,14). These reactive conditions are not accompanied by an inflammation of the mucosa and therefore deserve to be seen as a separate category namely rhinitis like conditions.

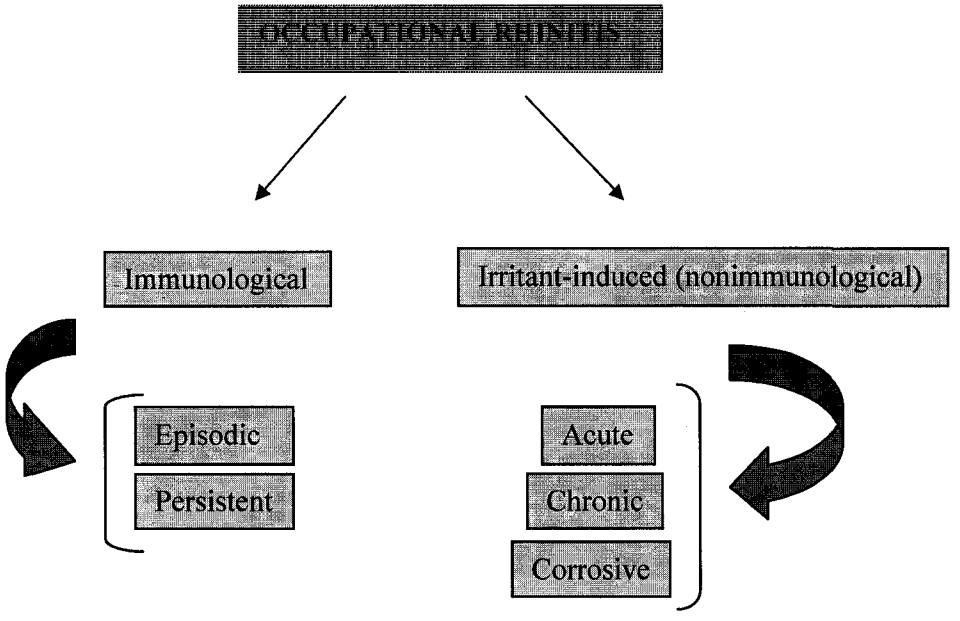
Occupational rhinitis

The difficulties in formulating a classification of occupational rhinitis arise from inaccuracies in the initial classification of occupational rhinitis as a type of rhinitis within the broad general classification of rhinitis. Traditionally, rhinitis has been classified into three main types: allergic (seasonal or perennial), infectious (acute or chronic) and "other" in which occupational rhinitis is listed along with idiopathic rhinitis, hormonal rhinitis, drug-induced rhinitis, nasal polyps, and primary atrophic rhinitis (15). In such a classification, allergic causes of occupational rhinitis are not taken into consideration and occupational rhinitis is relegated to being an isolated type of non-allergic, non-infectious rhinitis. This clearly does not correspond to reality. A more appropriate although still incomplete classification of occupational rhinitis has been suggested by the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology who developed guidelines for diagnosis and management of rhinitis (16). This agency classifies rhinitis in three main categories: (i) allergic rhinitis, (ii) non-allergic rhinitis and, (iii) conditions that mimic symptoms of rhinitis. This classification includes occupational rhinitis under both the allergic and non-allergic rhinitis. When the agency defines occupational rhinitis, it subclassifies it into allergic and nonallergic (16). Instead of classifying occupational rhinitis as allergic and non-allergic, we propose a classification inspired by that used for occupational asthma (17). It is based on induction mechanism and clinical presentation. This classification is summarized in Figure 2.

According to mechanism of induction, occupational rhinitis may be classified into: (i) immunological and (ii) irritant-induced (nonimmunological) rhinitis.

Immunological occupational rhinitis is characterized by the acquisition of sensitization. This category includes occupational rhinitis caused by high-molecular-weight agents and low-molecular-weight agents. High molecular weight agents are protein-derived agents of biologic origin (e.g, animal, plant, microbial); low molecular weigh agents are chemicals (e.g, natural, synthetic, metals) (11). High molecular weight agents produce occupational rhinitis with a latency period mainly through an IgE-dependent mechanism. In this well known mechanism the interaction between the antigen and the IgE leads to mast cell degranulation and release of inflammatory mediators. Low molecular weight agents are substances that are too small to be immunogenic by themselves. Therefore, they cannot act as antigens. However, it has been observed that some of them (e.g, isocyanates, anhydride acid, platinum salts) can combine with a protein to form an hapten-protein conjugate that can behave like a antigen and launch a full IgE allergic response (3).

Figure 2. Types of occupational rhinitis



The classification in Figure 2 makes provision for different clinical presentations of the immunological occupational rhinitis. It divides the immunological occupational rhinitis into two subcategories, episodic and persistent. The episodic category represents those cases with a recurrent or periodical pattern of symptoms. In contrast, persistent immunological occupational rhinitis would include those cases with persistence of symptoms even when the worker is away from the exposure at work.

This subdivision deserves additional considerations. Traditionally, the otolaryngological literature classifies rhinitis into two types based on duration of symptoms: acute and chronic rhinitis. Acute types correspond to those cases of rhinitis that resolve completely. The most well known example is the common cold. Chronic rhinitis comprises all those other cases of rhinitis that independently of their mechanism of induction have a chronic course with frequent relapses and exacerbations. Allergic rhinitis is commonly regarded as a chronic respiratory disease because it can be treated and controlled but not cured. Therefore, nasal symptoms in allergic rhinitis manifest over time depending on the degree of sensitization and the persistence, frequency and intensity of the exposure. In this sense, all cases of immunological occupational rhinitis are chronic and may have an episodic or persistent pattern of clinical presentation. Another plausible clinical scenario is the progression during the natural history of the disease from the episodic to the persistent type due to poor environmental and medical control of the rhinitis. This leads to irreversible changes in the nasal mucosa which will manifest essentially as nasal obstruction.

The category irritant-induced occupational rhinitis includes cases of occupational rhinitis caused by low molecular weight agents in which nonallergic less well-known pathogenic mechanisms are involved. We distinguish three subcategories: acute irritant, chronic irritant and corrosive. Clinically, this type of occupational rhinitis would take the form of an acute or a chronic rhinitis secondary to varied types of chemicals found at the workplace.

The sub-category acute irritant includes those cases of rhinitis in which a previously healthy, asymptomatic worker develops nasal symptoms after exposure to irritants in circumstances such as inhalational accidents. This category can have two clinical patterns depending on the resolution or persistence of the nasal symptoms. In the first pattern the patient becomes asymptomatic after a period of up to 12 weeks. The second pattern implies the lack of resolution of the nasal symptoms after 12 weeks and their persistence for months and even years. This second pattern also implies that the patient may progress from an acute to a chronic form of irritant-induced occupational rhinitis. This classification of irritant-induced occupational rhinitis as acute or chronic based on number of weeks of duration has not been defined arbitrarily. It is borrowed from the parameters that define rhinosinusitis as acute and chronic based on duration of symptoms established by a Task Force of the European Academy of Allergology and Clinical Immunology (EAACI) in a position paper on Rhinosinusitis and Nasal Polyps (18). It is not erroneus to use these parameters considering the close link between the nose and the sinuses since there is contiguity of the mucous membranes. Although it is possible to observe cases of rhinitis without involvement of the sinuses, it is

rare to observe a case of sinusitis without a concomitant rhinitis. Even if there are no studies to support this affirmation, we venture to affirm that the compromise of sinuses in occupational rhinitis of all types is highly likely.

One suggested nonimmunological mechanism for acute and chronic irritant occupational rhinitis is that the exposure to an irritant leads to the release of a neuro-sensory transmitter called substance P and other mediators of inflammation that originate from nerve endings and trigger a neurogenic inflammatory response (19, 20). This mechanism has been proposed in the occurrence of the Reactive Upper Airways Dysfunction Syndrome (RUDS). RUDS is a reaction of the upper respiratory tract analogous to the Reactive Airways Dysfunction Syndrome (RADS) of the lower respiratory tract (21). RADS is an asthma-like syndrome classified as an irritant-induced type of asthma without a latency period. The condition is observed in persons acutely exposed (inhalational accident) to high levels of an irritant. The main features of the syndrome are the rapid onset of respiratory symptoms (within 24 hours after the exposure) that mimics an asthma crisis, and the persistence of respiratory hyperreactivity for months and even years in individuals without preexisting respiratory illness (22, 23). Analogously, RUDS may be defined as a form of acute irritant-induced rhinitis (without a latency period) followed by a hyperreactivity of the nose with persistent symptoms. As in RADS, symptoms in RUDS are manifested by individuals without preexisting upper respiratory tract illnesses who are exposed to high levels of an irritant and in whom persistent symptoms and perhaps sustained increased nasal airway resistance are observed despite the avoidance of the irritant. (19, 24, 25).

The sub-category chronic irritant (fig.2) may include subjects exposed to irritants in different forms (e.g, fumes, dust, vapours, gases) such as chlorine, ammonia, glutaraldehyde and wood dust that entertain chronic nasal symptoms. In contrast to RUDS, the characteristic of this subtype of occupational rhinitis is the insidious progressive instalment of rhinitis symptoms without a history of an acute exposure. There are a number of exposures that have been associated with chronic nasal symptoms in which the specific offending agent cannot be identified. In these cases symptoms may be due not only to a single irritant agent but to a mixture of several irritants. These exposures can take place for example in offices in the use of photocopiers and/or laser printers (26, 27) and also in offices with air-conditioning systems.

Although a nasal septal perforation has always been considered as a plausible outcome of exposures to metals such as chromium, nickel, copper, and arsenic, subjects with such a nasal problem have never been categorized to the best of our knowledge as having a type of rhinitis. The sub-category corrosive occupational rhinitis intends to cover those cases of occupational rhinitis secondary to exposure to corrosive chemicals in which can be observed nasal ulceration and/or nasal septum perforation (26, 28). We consider that the development of a nasal septal perforation of occupational origin entails a history of rhinitis that could be classified as chronic due to an insidious and gradual instalment of symptoms (e.g, nasal obstruction, dryness, formation of crusts, bleeding) with progression to ulceration and ultimately in many cases, to perforation of the nasal septum. This category can be considered a chronic

form of irritant induced occupational rhinitis but we propose to categorize it as a distinct form to take into account its specific clinical feature.

Conclusions

The appropriate diagnosis and management of occupational rhinitis should rely on both a workable definition and a well-structured classification of this respiratory disorder. In this paper, we proposed new elements for discussion on the definition and classification of occupational rhinitis. They borrow to the widely accepted definition and classification of occupational asthma. They also spouse the postulates of the "United Airways Disease" model, a model that presents both disorders rhinitis and asthma as two clinical manifestations of a single disorder in which allergic and non-allergic mechanisms are involved. The link between rhinitis and asthma is recognized and well established in the general population. There is evidence that supports its presence at the workplace as well.

The present classification as we propose is not exempted of limitations. It can be challenged and improved with new evidence of pathogenic mechanisms. We acknowledge that the pathogenic mechanisms of irritant-induced occupational rhinitis have been less investigated and nowadays are the object of research and discussion. In addition, overlapping nasal reactions between occupational rhinitis categories and with other nasal pathologies is highly likely and can create diagnostic difficulties. Likewise, the characteristics of the other categories of rhinitis that can be observed occurring at the workplace namely, work-aggravated rhinitis and rhinitis-like conditions should be the object of research in the future.

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CHAPTER SEVEN

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Categorizing nasal septal perforations of occupational origin as cases of corrosive rhinitis
Am J Ind Med. 2007; 50 (2): 150-3

Abstract

Background. In clinical practice a perforation of the nasal septum secondary to an occupational exposure to corrosive chemicals is not considered a sequel of rhinitis.

Methods. Relevant articles published in the last 26 years were searched and retrieved from Pubmed.

Results. Patients with nasal septal perforations of occupational origin show a history of rhinitis with a gradual installation of symptoms and damage of the nasal mucosa progressing to ulceration and ultimately to perforation of the nasal septum.

Conclusions. Patients with nasal septal perforations of occupational origin exhibit the clinical and histopathological features of rhinitis whereby they should be categorized as rhinitics. This rhinitis should be considered as a type of irritant-induced occupational rhinitis and classified as corrosive rhinitis.

Introduction

The nasal septum is a structure made partly of bone and partly of cartilage that divides the nose in two nasal cavities. The nasal septum contributes to the support of the nose and also to its external shape. The cartilaginous part or septal cartilage is covered by a mucoperichondrium that provides the necessary blood supply. A nasal septal perforation corresponds to a hole within the cartilaginous, the bony portion of the nasal septum or both. The cartilaginous component or septal cartilage is the site where perforations are observed more frequently (Diamantopoulos and Jones 2001).

Nasal septal perforation is a clinical sign whose occupational origin is often overlooked. The aetiology of nasal septal perforations has been and continues to be a great challenge for otorhinolaryngologists despite notorious advances in methods of investigation in the last 10 years. General otolaryngology textbooks refer to nasal septal perforations as a plausible clinical sign of chronic granulomatous infectious and non-infectious diseases or of autoimmune diseases. The reason is that a nasal septal perforation is not a disease by itself but the expression of a variety of conditions that can affect the nose.

When present a nasal septal perforation generates great concern in both the physician and the patient. For the physician, the aetiology of septal perforation may remain obscure even after following the recommended approaches to diagnosis and its management either medical and/or surgical is not exempt of difficulties. For the patient he will have to deal with the uncertainty of the cause of the perforation that includes several potential medical conditions and the long-term treatment and follow up. To date there is

no diagnosis under which to categorize a patient with a perforation of the nasal septum that results from an exposure at work. The objective of this paper is to provide evidence from research studies that workers with a nasal septal perforation secondary to exposure to corrosive chemicals should be considered as having a rhinitis and discuss the term corrosive rhinitis as a type of occupational rhinitis to categorize such patients.

Methods

Relevant peer-reviewed studies addressing the aetiology and diagnosis of nasal septal perforations as well as clinical aspects of occupational rhinitis were searched and selected from the PubMed database for articles published from 1980 to 2006 using the following key words: nasal septal perforation, occupational, occupational rhinitis.

Etiologic considerations

The causes of nasal septal perforations are heterogeneous as shown in table 1. However, despite the fact that these causes are well known many cases are ultimately categorized as idiopathic. A retrospective review of 74 cases of patients presenting either a nasal septal perforation or nasal ulcer showed that 47% of them were considered idiopathic (Diamantopoulos and Jones 2001). This elevated percentage reflects simply the difficulties in identifying a specific aetiology to this clinical condition.

Table 1. Selected examples of causes of nasal septal perforations by category

- **Infectious**: tuberculosis, syphilis, leprosy
- **Traumatic**: post-nasal surgery, nasal injury, nose picking, nasal septum cauterizations, foreign bodies
- **Autoimmune**: systemic lupus erithematosus, rheumatoid arthritis, Wegener granulomatosis
- **Inhaled drugs**: cocaine, nasal corticosteroids, long-term use of topic alfa agonists
- **Occupational**: chromium, arsenic, nickel, copper
- **Malignancies**: carcinomas, T-cells lymphomas, crioglobulinemia
- **Idiopathic**

The occupational origin of nasal septal perforation

Causative agents: corrosive chemicals

Exposure to corrosive chemicals constitutes an important hazard in the workplace. Major classes of corrosive chemicals include strong acids and alkali, oxidizing and dehydrating agents. The main feature of these highly reactive substances is their capacity to produce irreversible damage to living tissues. A definition of these agents states by Occupational Safety & Health Administration (OSHA) states that they are "chemicals that cause visible destruction of, or irreversible alterations in, living tissue by chemical action at the site of contact". This means that the contact with corrosive chemicals entails a risk of serious consequences for health. The respiratory system is one of the potential routes of exposure to these chemicals. Thus, damage to either the upper respiratory tract and the lower respiratory tract or both is highly likely after exposure to corrosive chemicals. Under the above premise any corrosive chemical has the potential to cause an irreversible damage to the nasal mucosa of the type perforation of the nasal septum. However, in spite of the fact that the list of corrosive chemicals is long, except for chromium, there

is little evidence that these chemicals have actually been reported as causing nasal perforation in workers exposed. This lack of evidence may be due to the scarce epidemiological research that has been conducted on the effects provoked by corrosive chemicals in the internal nose. Nevertheless in occupational health practice exposure to chromic acid mist in the form of hexavalent chromium is a good example of a well-established and long recognized cause of nasal septal perforation secondary to a corrosive chemical in the electroplating industry. The magnitude of this problem becomes noticeable in cross-sectional studies conducted in workers exposed to this corrosive chemical.

A survey conducted in workers exposed to chromium in electroplating factories in Taiwan showed a prevalence of 20% (16/79) and 53% (42/79) respectively of nasal septal perforations and nasal septum scar formation or ulceration in workers exposed to chromium (Lin et al. 1994). The prevalence of nasal septal perforation and nasal septum ulcer was 31% and 39% respectively in a cohort of workers exposed to chromium in Taiwan (Kuo et al. 1997). Chronic exposure to low-level hexavalent chromium was the cause of 11 nasal septal perforations and 51 nasal septum ulcerations detected in a cohort of Korean welders (Lee et al. 2002). Exposure to other metals such as nickel, copper and arsenic is also reported as causing nasal septal perforation in populations of exposed workers (NIOSH 2005).

Corrosive rhinitis as a category of occupational rhinitis

In clinical practice a perforation of the nasal septum resulting from exposure to a corrosive chemical at the workplace is not considered a sequel of rhinitis

in spite of the fact that its natural history exhibits a history of rhinitis. Workers exposed to corrosive chemicals can manifest symptoms such as nasal obstruction, dryness, formation of crusts and bleeding similar to the ones presented by subjects who suffer from occupational rhinitis due to other irritants and allergens (Brisman et al.1998; Kraus et al.2002; Kuo et al.1997; Lin et al.1994). Later in the natural history of this condition, an irreversible damage of the nasal mucosa progressing from ulceration to perforation of the nasal septum (Lee et al.2002) has been observed along with accentuation of the symptomatology. Another study showed an association between the degree of exposure to chromium calculated as lifetime exposure index to chromium and the severity of nasal septal lesions by observing the progression from erosions and ulcerations to scar formation and nasal septal perforation (Lin et al.1994).

Subjects with nasal septal perforations of occupational origin have the histopathological features of any rhinitis namely, inflammation of the mucosa confirmed by nasal biopsies and they report symptoms of rhinitis as a manifestation of such an inflammation. This is confirmed by studies that have observed the histopathology of cases of nasal septal perforations (Diamantopoulos and Jones 2001; Murray and McGarry 2000) and by epidemiological studies that have assessed the presence of upper respiratory tract signs and symptoms in groups of workers exposed to corrosive chemicals (Grasel et al.2003; Kitamura et al.2003; Kuo et al.1997; Lindberg and Hedenstierna 1983). To take into account the above a subject with a nasal septal perforation secondary to exposure to a corrosive chemical should be

diagnosed as having a rhinitis and this rhinitis be categorized as corrosive considering the effects of the agent on the nasal mucosa. Corrosive rhinitis should include cases of nasal septal ulceration and/or perforations observed as a consequence of exposures to corrosive chemicals at the workplace. Occupational rhinitis is an emerging domain in occupational health (Gautrin et al.2006). Many aspects related to this disease such as its definition and classification are nowadays the object of discussion (Castano et al.2006). A recent definition of occupational rhinitis states that it is "a type of rhinitis characterized by intermittent and sometimes permanent nasal airflow limitation due to causes and conditions attributable to the work environment" (Castano and Thériault 2006). Corrosive rhinitis meets this definition criterion and as such should be considered a rhinitis of occupational origin. A recently proposed classification of occupational rhinitis based on its pathogenic mechanism considers two main categories namely, immunological induced and irritant-induced occupational rhinitis. Corrosive rhinitis is one of the types of the irritant-induced category (Castano and Thériault 2006).

Evidence from histopathologic observations

Histopathologically the term rhinitis entails inflammation of the mucous membrane of the nose. Biopsies of nasal mucosa performed on septal perforations confirm that in most cases the main finding is inflammation. Murray et al examined retrospectively the results of biopsies from 63 patients with nasal septal perforations to assess their clinical value in establishing an etiologic diagnosis. In sixty-one patients (97%) the biopsy was reported as "simple/chronic inflammation" (Murray and McGarry 2000). With the same purpose, Diamantopoulos et al evaluated retrospectively 74 patients of whom

54 had a nasal septal perforation and 20 an ulcerative lesion of the septum. Findings from biopsy showed inflammation (acute, chronic, acute to chronic) in 22 patients, trauma in 9 and nonspecific findings in all the remaining cases (Diamantopoulos and Jones 2001). The study also reports that in 3 cases an occupational exposure (not specified) could be identified as the aetiology of the nasal mucosa inflammation. Grasel et al evaluated the effect of occupational exposure to sulphuric acid mists on the nasal mucosa of workers in the galvanizing industry in Brazil. This study showed significant differences between exposed workers and subjects without antecedents of exposure to industrial airways irritants (controls) with regard to squamous atypia, mild dysplasia, thickness of the basal membrane, inflammatory infiltrate in the lamina propria and neutrophils infiltration (Grasel et al.2003). Regardless of the fact that studies examining the histopathology of nasal septal perforations are scant, it is clear from the evidence available that inflammation of the nasal mucosa is a key feature of this condition.

Evidence from clinical observations: symptoms and signs of rhinitis in workers at risk of nasal septal perforations

Patients exposed to corrosive chemicals complain of common nasal symptoms such as nasal obstruction, sneezing and itching as do patients with a rhinitis of any aetiology. They also complain of other less common nasal symptoms such as dryness, epistaxis, formation of crusts and impairments of the sense of smell. Workers exposed to chromic acid in electroplating factories in Taiwan reported rhinorrhea (35%) and nasal obstruction (15%) as a result of the exposure at work (Kuo et al.1997). Welders exposed to low-level hexavalent

chromium complained of stuffiness and epistaxis in a study conducted in Korea (Lee et al.2002). Nasal obstruction, rhinorrhea and epistaxis were more prevalent in workers performing chromium electroplating as compared to workers performing aluminum electroplating (Lin et al.1994). Symptoms of nasal irritation were commonly reported by workers exposed to 1 microgram/m3 of chromic acid or more as compared to controls (Lindberg and Hedenstierna 1983). Hyposmia expressed by a significant increase in olfactory threshold has been reported in workers exposed to chromium as compared to non-exposed subjects (Kitamura et al.2003). Nasal symptoms such as itching, sneezing, burning, rhinorrhea and epistaxis along with endoscopic findings of hyperaemia, ulcerations and pale mucosal patches were documented in workers exposed to sulphuric acid mists (Grasel et al.2003). These reports confirm that subjects occupationally exposed to corrosive chemicals exhibit symptoms and signs that are observed among patients with occupational and nonoccupational rhinitis.

Pathway to establish a diagnosis of corrosive rhinitis

The diagnosis of corrosive rhinitis should be considered a diagnosis of exclusion due to the multiplicity of etiologic categories and their dissimilar prognosis. The following are recommendations from the authors for occupational health physicians to establish a diagnosis of and categorize a case as corrosive rhinitis:

- Suspect the presence of a nasal septal perforation if a worker persistently or recurrently exposed to corrosive chemicals has a history

of persistent rhinitis symptoms including frequent crusting and bleeding.

- Determine the integrity of the nasal septum by performing anterior rhinoscopy. If uncertain of the integrity of the nasal septum refer the worker for an otolaryngologist consultation
- Exclude all nonoccupational causes of nasal septal perforations if a perforation of the septum is detected
- Catalogue the case as corrosive rhinitis if no specific aetiology is found and there is a clear antecedent of exposure to a corrosive chemical at the workplace.

Conclusions

A nasal septal perforation is a plausible outcome of occupational exposures to corrosive chemicals that has significant medical implications. Therefore, it is important that patients presenting nasal septal perforations of occupational origin have a diagnosis. This paper proposes that clinical and histopathological observations justify the categorization of patients presenting a nasal septal perforation of occupational origin as rhinitics. In addition, subjects presenting with this outcome should be more precisely categorized as having corrosive rhinitis due to the irreversible damage to the nasal mucosa and septum. Furthermore, since its origin is occupational this type of rhinitis becomes an occupational rhinitis and should be accounted for in a comprehensive classification of occupational rhinitis.

The prevalence of nasal septal perforations in workers chronically exposed to hexavalent chromium is high. It may also be elevated among workers exposed

to other corrosive chemicals but no empirical data exist on the frequency of nasal septal perforation among the chemically exposed workers. Occupational health professionals, general medical practitioners and otorhinolaryngologists should search for antecedents of exposures to corrosive chemicals at the workplace when they assess patients with nasal septal perforations. It is not likely that many cases of idiopathic nasal septal perforations are related to unrecognized occupational exposures to corrosive chemicals. More epidemiological research on corrosive rhinitis is encouraged to better document the occupational origin of this condition.

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CHAPTER EIGHT

General discussion, implications and future perspectives

This chapter discusses issues related to the validity of the results presented in this thesis avoiding repetition of information, concepts and discussion already covered in the corresponding sections of each article that compose the thesis. The chapter also comments on the spectrum of implications of the results and suggests areas of related research that merit further exploration.

Considerations on the validity of the study

This subsection addresses some potential threats to the validity of the study described in Chapter 1 in terms of study design and operational procedures.

Methodological considerations

In this study we diagnosed occupational rhinitis and occupational asthma by challenging patients with the suspected occupational agent. The methodology of diagnosing occupational asthma by performing specific inhalation challenges is well standardized and constitutes the gold standard for the diagnosis of this disease. By contrast, there are no accepted standards for the procedure of nasal challenges with occupational agents. Nevertheless, challenging with a causal agent currently represents the recommended approach to diagnosing occupational rhinitis. The nasal assessment was carried out in parallel to the assessment of the lungs using the same specific inhalation challenge method. This approach was in fact necessary to achieve the main study objective, i.e. demonstrating a concomitant reaction in the nose and lungs after exposure to occupational agents.

The assessment of nasal responses during the challenge included objective measurements of nasal patency and inflammation by acoustic rhinometry and

nasal lavage respectively. These techniques have recognized validity but their reproducibility in the setting of occupational challenges was unknown. Accordingly, we examined the reproducibility of these techniques during this research. The results shown in Chapter 2 and Chapter 3 demonstrated that both techniques were sufficiently reproducible to be used as main investigative tools to monitor the nasal reaction during the challenge.

A distinctive physiological feature of the nose is the presence of a nasal cycle. This cycle comprises the normal periodic congestion and decongestion of the nasal mucosa and turbinates. Normally, the airflow through the nasal passages is asymmetrical due to alternating changes in nasal resistance in each nasal cavity. However, the total nasal resistance to airflow remains somewhat constant, as changes between the nasal passages tend to be reciprocal. As a result, people are usually unaware of this physiological phenomenon. Accounting for the nasal cycle during nasal challenges is crucial. Nasal challenge methods should involve a bilateral exposure of the nose in order to minimize the effects of the nasal cycle. In addition, outcome measurements of nasal patency should represent a total combined quantitative assessment of both nasal cavities. Our study used two challenge methodologies, i.e. the closed circuit method and the realistic method (described in Chapter 1); in both cases the nose is challenged bilaterally. The monitoring of nasal patency with acoustic rhinometry in all cases involved bilateral measurements to calculate the total nasal volume and the total minimum cross-sectional area.

We also wanted to include information on the nasal reaction to the challenge by methods other than acoustic rhinometry to make comparisons between different methods and support and complement our findings with acoustic rhinometry. We therefore monitored the nasal response during challenge using two additional means: by anterior rhinoscopy (physical examination of the nose) and by using a visual analogue scale completed by the patient. In a subgroup of study subjects we also assessed the inflammatory response of the nose to the challenge by a nasal lavage technique. Assessment of inflammation by nasal lavage is a particularly useful complement to the information obtained by acoustic rhinometry.

Results from subjective methods (rhinoscopy, visual analogue scale) are not presented in this thesis and will be the subject of other article comparing them to objective measurements (acoustic rhinometry). Briefly, we observed no correlation between the bilateral subjective perception of nasal obstruction and acoustic rhinometry outcomes. Anterior rhinoscopy showed a good and significant correlation with acoustic rhinometry during the first hour post-challenge on the session with the active agent; the correlation assessing baseline parameters on the control and active day was significant but weak. These findings prevent the utilization of anterior rhinoscopy as the main tool to monitor nasal responses during specific inhalation challenge. The assessment of changes in nasal patency during a control day must be as accurate as possible because it determines if the evaluation should continue with the challenge with the active agent by ruling out nonspecific nasal hyperreactivity among subjects.

Our preliminary observations on the correlation of investigative methods used in this research highlight the importance of using objective measurements to assess nasal obstruction as was the case in this thesis.

Although acoustic rhinometry measurements were sufficiently reproducible in our hands, the method may have some limitations if particular attention is not paid to technical and operating procedures. For example, proper positioning of the sound wave is essential to perform the test and obtain accurate measurements. In our study, the same technician was responsible for performing the test over the study period. She was trained for three months before starting the formal evaluation of patients. We also followed a rigorous protocol to perform acoustic rhinometry. The same equipment was used throughout the study and calibrated every day. Potentially confounding variables that may have influenced the measurements with this technique were considered in the protocol. Laboratory temperature and humidity conditions were kept constant; patients stayed in the laboratory during the entire day of evaluation to avoid external environmental exposures; and patients were instructed to restrain from physical activity and to avoid eating foods with some potential to induce nasal symptoms. The main sources of confounding (nasal conditions that may mimic or coexist with a rhinitis and subjects under regular medications for nasal symptoms) were controlled by applying protocol exclusion criteria.

In this study occupational rhinitis and occupational asthma were defined on the basis of objective findings that provide some protection against

information bias. However, misclassification derived from errors in classifying specific inhalation challenges as positive or negative for occupational rhinitis was not unlikely in this study. We attempted to eliminate this source of bias by being rigorous in implementing our diagnostic protocol and having ample control of the study design. The evaluation of all subjects included a control day in order to assess nonspecific nasal hyperreactivity. During this session subjects were challenged with lactose and xylol for high-molecular weight or low-molecular weight agent, respectively. These substances have been used as sham exposure in our hospital for several years for the assessment of nonspecific bronchial responses in the investigation of occupational asthma. With this approach, seventeen control sessions were categorized as positive and therefore the subjects were excluded from the analysis.

The criterion for categorizing a specific inhalation challenge as positive was a decrease in Vol2-5 of $\geq$ 30% after exposure to the active agent in the absence of a positive reaction during the control day. The selection of this threshold was not arbitrary; it was based on the analysis of the reproducibility of acoustic rhinometry measurements (Chapter 2) and the examination of the variation of nasal volume during the control day among all study subjects. Few studies have reported threshold values for acoustic rhinometry to indicate when a nasal reaction should be considered positive or negative. Pirila and Nuutinen [1] challenged a group of allergic farmers and controls to a cow allergen and determined a threshold value of a 15% decrease in minimum cross-sectional area when the observation time after challenge was 30 minutes and of 30% for an observation time of 60 minutes. Ganslmayer et al., [2]

challenged allergic rhinitis patients and nonatopic volunteers with allergens and determined a reaction threshold of 29% decrease in minimum cross-sectional area. Our threshold value based on changes in nasal volume compares to those determined by Ganslmayer and Pirila for minimum cross-sectional area. Nasal volume was selected as the parameter to use under the assumption that volume change more realistically reflects mucosal changes secondary to congestion than acoustic rhinometry parameters based on cross-sectional estimates [3]. However, we also measured the minimum cross-sectional area. Both parameters have demonstrated a good correlation in published studies. We also observed a good and significant correlation between the two parameters during both the control and challenge sessions, but the correlation was stronger during the challenge day. This suggests that under relatively stable conditions, like those expected during a control day, the two parameters do not correlate as well as under conditions in which stronger physiological reactions are expected. The observed mean maximum percentage decrease during the control and challenge day was greater when measuring the Vol2-5 than the MCA. This suggests that Vol2-5 is a more sensitive parameter to monitor changes during SIC than MCA.

As mentioned above, the purpose of the control day was to assess subjects for nonspecific nasal responses. In general, we do not expect a major reaction of the nose during this day apart from the physiological nasal cycle. However, there might be some potential for a carryover or residual effect if some effect on the nasal mucosa after the challenge with the control agent persists in time influencing the response on the subsequent challenge day with the active

agent. We consider that a significant carryover bias did not occur in this study because: first, subjects who showed a significant reaction by acoustic rhinometry during the control day were excluded from the study; second, by study design, challenges with the control and active agents were carried out on different days with at least 24 hours of time interval; and third, the analysis of the reproducibility of acoustic rhinometry measurements described in Chapter 2 showed that there were no differences between pre-exposure control and active challenge baseline measurements in consecutive sessions; this indicates that the time interval between sessions was sufficient to reproduce similar baseline nasal conditions.

Considerations regarding study subjects

This study involved a purposive sampling strategy to target our study population, which consisted of workers referred to the Chest Department of Hôpital du Sacré-Coeur de Montréal for investigation of occupational asthma. Thus, study subjects were recruited from sequential workers who met the criteria for probable occupational asthma and had work-related exposure to high- and low-molecular weight agents.

It is unclear how representative our study subjects are of all workers with work-related asthma symptoms. It is likely that we missed young workers with a history of asthma symptoms that developed rapidly after starting a job, and who for this reason, may have left their jobs before a diagnosis of occupational asthma was made. Prospective cohort studies have shown that specific immunological sensitization to high molecular weight agents and work-related asthma symptoms mostly, though not exclusively, appear during the first years

of exposure [4]. Moreover, cohort studies conducted in young apprentices have concluded that health-related self-selection out of an apprenticeship with exposure to HMW agents is likely to occur and to cause an attrition bias in that context [5].

Our population comprised workers with a relatively long duration of exposure which may have introduced a bias because of the "healthy worker effect," as those with more severe lower respiratory tract symptoms were more likely to have been removed from exposure. Therefore, those workers who stay at work exposed to noxious agents are likely to be less affected. In the context of this study, it was also possible that more severe asthma cases tended to be referred, as well as those from known high-risk occupations.
We do not know if the association we found between occupational asthma and occupational rhinitis might be influenced by asthma severity. Nevertheless, this association would have been underestimated in our results if such an association were more likely in cases of work-related asthma symptoms severe enough to justify leaving a job quickly.

Additional considerations on the results of the study

Our study made it possible to better characterize the "united airways disease" model. We provided objective evidence in support of the model but also on its limitations. In addition, the findings constitute also the first objective evidence of the applicability of the "united airways disease" model to rhinitis and asthma of occupational origin. Epidemiological surveys show that the expression of rhinitis symptoms in subjects with asthma is expected in almost all cases, which is indeed highly suggestive of the presence of a unique

disease. Our study objectively demonstrated that in some subjects, it is possible to observe a clinically significant joint reaction of the nose and lungs that means they should be considered to have both occupational rhinitis rhinitis and occupational asthma. However, it is also possible to observe isolated clinically significant reactions in either the nose or lungs that means a subject should be considered to have only occupational rhinitis or occupational asthma. This means that not all subjects with documented occupational rhinitis will inevitably develop occupational asthma. In the discussion section of Chapter 1 some interpretations of these findings were described.

To explain the cases of occupational rhinitis alone we suggested a "stepwise sensitization" process in which the nose is sensitized initially as the first target organ, followed by sensitization of the bronchi over time. However, we cannot be absolutely sure that a physiological reaction did not occur in the bronchi in those cases with occupational rhinitis alone as the means we used to assess changes in the lower airways (spirometry, induced sputum, methacholine test) are less sensitive than more invasive methods such as bronchoscopy with bronchoalveolar lavage and biopsies.

Although the progression from occupational rhinitis to occupational asthma has been documented [6] it certainly does not occur in all circumstances confronting the hypothesis of the "allergic march" model. In the general population it is well established that only a proportion of patients with allergic rhinitis develop asthma [7;8]. Also, occupational longitudinal epidemiological studies have failed to demonstrate a clear "allergic march" [9]. Moreover, it is not unusual to observe discordance between specific sensitization and manifestation of disease; a subject can develop work-related rhinitis and/or

asthma without demonstrable sensitization [9]. Thus, it is realistic to speculate that more factors are involved in the pathogenesis and natural history of occupational rhinitis. An alternative or complementary hypothesis to explain the isolated expression of occupational rhinitis in some of our study subjects entails an increased local production of immunoglobulin E (IgE) in the nose. It has been demonstrated that the nasal and bronchial mucosa by themselves have the capability to induce an IgE-mediated immunological response [7]. Local production of IgE has been detected in nasal B-cells of patients with allergic rhinitis. [10;11] In one study cultured functional nasal B-cells were able to synthesize IgE. [12] Increase in specific IgE in bronchoalveolar lavage has been demonstrated after segmental allergen challenge in atopic asthmatics. [13] Local synthesis of IgE in the nasal mucosa may involve the expression of ε germ line transcripts for the ε heavy chain of IgE.[14]

There are also anatomical and physiopathological differences that account for a more accentuated physiological reaction in the nose than in the bronchi after exposure to allergens and irritants promoting the appearance of symptoms and disease first in the nose or only in the nose. The most obvious difference is that the nose is more exposed than the bronchi. Hence, it becomes the first barrier against inhaled noxious substances. Moreover, the physiological changes occurring in the nose and the bronchi after exposure to allergens or irritants (e.g, nasal congestion, bronchoconstriction) comprise different physiopathological events. Thus, in clinical practice we assess different physiological responses, a reduction in airway calibre of a partly rigid anatomic structure (smooth muscle) in the bronchi and a circulatory event (venous congestion) in the nose. Consequently, the nose is a more

dynamic and more sensible anatomic structure than the bronchi. Within the nose changes take place continuously to provide good conditioning to the inspired air that travels to the lower respiratory tract. This dynamism is reflected in a greater variability of functional parameters during quiescent conditions and becoming more accentuated under more challenging conditions, as demonstrated in our studies.

Implications and future perspectives

Our research findings add substantially to existing knowledge on occupational rhinitis. These findings have implications for the spheres of clinical and public health medicine that may benefit workers, clinicians, employers, workers' compensation agencies, occupational health professionals and agencies. Our research developed and tested a protocol to diagnose occupational rhinitis based on objective physiological measurements of nasal patency and nasal inflammation. This protocol can be used to diagnose this disease in patients with a history of work-related rhinitis symptoms alone or in association with work-related asthma symptoms. For clinicians, the availability of a valid method to diagnose occupational rhinitis will permit early detection and management of this condition, which may have an impact in the prevention of the development of occupational asthma in populations of workers in high-risk occupations.

The results of this study highlight the importance of assessing the nose in subjects with asthma symptoms. This is particularly important in the context of occupational medicine. As we have demonstrated, occupational rhinitis is

underdiagnosed. Subjects with a history of work-related asthma symptoms should be systematically investigated for the presence of rhinitis symptoms even if they are not complaining of nasal symptoms. Moreover, a diagnosis of occupational rhinitis should be considered in all subjects with probable occupational asthma undergoing specific inhalation challenge for confirmation of the disease and also complaining of nasal symptoms in order to, if feasible, also document with objective means nasal responses to the challenge. A confirmed diagnosis of occupational rhinitis in these patients should be considered as supportive evidence for a positive diagnosis of occupational asthma. A patient diagnosed with both conditions should be considered more disabled than a patient with occupational asthma alone.

A diagnosis of occupational rhinitis alone entails a different situation. Contrary to occupational asthma, many legislative and compensation aspects of occupational rhinitis have not been defined and established. In many cases a patient with a diagnosis of occupational rhinitis will have to continue working and continue to be exposed to an agent to which he has been demonstrated to be sensitized or sensitive. This means that nasal symptoms may eventually worsen with time and raise concern of a higher risk for later developing occupational asthma. A comprehensive legislation policy regarding occupational rhinitis is therefore desirable and necessary.

For workers' compensation boards, the benefit of our research is that they can rely on a valid method to assess workers claiming compensation for occupational rhinitis alone or associated with occupational asthma.

In the broad sphere of public-health, we hope that the findings of our study can be taken into account to propose and formulate an integrated management of occupational rhinitis and occupational asthma comprising preventive strategies and surveillance programs in the workplace to be implemented by industries.

Considering the findings of the study presented in this thesis, we believe that further research is needed to investigate why some workers develop only occupational rhinitis or occupational asthma while others develop both diseases. Research initiatives assessing the role of local production of IgE and IgG4 in the pathogenesis of occupational rhinitis and also determining the nasal leukocyte-lymphocyte phenotype by flow cytometry in these groups of subjects may provide some valuable information that will help answer that question in the future. Additionally, research efforts should continue to attempt to improve understanding of the mechanisms involved in the pathogenesis of immunological and irritant-induced occupational rhinitis, as well as investigating the inflammatory differences between allergic and non-allergic rhinitis and occupational rhinitis. The assessment of remodelling in subjects with different types of rhinitis including occupational rhinitis is an example of the type of investigations that should be carried out on this subject. Due to its clinical implications it will be very important to follow workers diagnosed with occupational rhinitis alone who continue being exposed in order to observe whether they develop occupational asthma in future. Along the same lines, when workers compensated for occupational asthma return for a reevaluation two years after diagnosis, those with occupational rhinitis could be reevaluated for persistence of that disease or changes. This may provide

information on the persistence of sensitization after cessation of exposure in those subjects who were no longer exposed.

Research tools are fundamental within the framework of research initiatives mentioned above. Thus, it is fundamental to continue improving, validating, and standardizing existing investigative methods to assess physiopathological changes occurring in the nasal mucosa such as nasal lavage, nasal brushing, and nasal biopsies.

The spectrum of "united airways disease" should be further investigated by also determining the involvement of the pharynx and larynx besides the nose and lungs as constituents of the respiratory tract. The role of the so-called vocal cord dysfunction syndrome associated with occupational exposures has yet to be determined. It would also be important to consider the role of new technology such as acoustic pharyngometry for the objective assessment of the pharynx and the larynx in subjects complaining of respiratory symptoms in the workplace.

Finally, considering the close link between occupational rhinitis and occupational asthma reported in this thesis, it would be important to conduct intervention studies with workers in high-risk industries for the development of respiratory symptoms with the aim of alleviating the effects of noxious occupational exposures on the respiratory tract.

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APPENDICES

Appendix A

Articles related to this thesis

The following two abstracts are from publications related to the topic of this thesis in which the author has participated as coauthor.

Moscato G, Vandenplas O, Gerth Van Wijk R, Malo JL, Quirce S, Walusiak J, Castano R, De Groot H, Folletti I, Gautrin D, Yacoub MR, Perfetti L, Siracusa A. Occupational rhinitis. Position Paper; European Academy of Allergology and Clinical Immunology (EAACI) 2007. Allergy. in press

Abstract

The present document is the result of a consensus reached by a panel of experts from European and non-European countries on Occupational Rhinitis (OR), a disease of emerging relevance which has received little attention in comparison to occupational asthma. The document covers the main items of OR including epidemiology, diagnosis, management, socio-economic impact, preventive strategies and medicolegal issues. An operational definition and classification of OR tailored on that of occupational asthma, as well as a diagnostic algorithm based on steps allowing for different levels of diagnostic evidence are proposed. The needs for future research are pointed out. Key messages are issued for each item.

Gautrin D, Desrosiers M, Castano R. Occupational rhinitis. Curr Opin Allergy Clin Immunol. 2006 Apr;6(2):77-8

Abstract

Purpose of review: This review updates existing knowledge on occupational rhinitis (OR) based on epidemiological and clinical research studies published from 2003 to 2005.

Recent findings: The review covers new developments on the pathophysiology, diagnosis, monitoring and management of OR. This article also provides updated information on the prevalence and incidence of both OR and work-related symptoms of rhinitis, as well as on aetiologic agents and personal risk factors associated with this condition.

Summary: OR is frequently underdiagnosed due to a lack of physician awareness. Diagnosis is suspected when symptoms occur in relation to work. Differentiating between immunological sensitization and irritation may be difficult. Given the high prevalence of rhinitis in the general population from all causes, objective tests confirming the occupational origin are essential. Measures of inflammatory parameters via nasal lavage and objective assessment of nasal congestion both offer practical means of monitoring responses. Growing experience with acoustic rhinometry and peak nasal inspiratory flow suggests that these methods will have an increasingly important role in monitoring and diagnosing in the future. Recent findings indicate that work-related rhinitis is to some extent preventable. Surveillance of sensitized workers may allow for early detection of OR.

Appendix B

Study subjects occupations and associated suspected agents

Occupations	*Agents*
With exposure to high-molecular weight agents	
Bakers, pastry makers, grain packing workers	Flour, wheat, barley
Laboratory workers, animal handlers	Animal proteins (rat, guinea pig, common pig, cat)
Food industry	Enzymes, tea, cinnamon, guar gum
With exposure to low-molecular weight agents	
Spray painters, paint shop	Diisocyanates (hexamethylene, diphenylmethane)
Solderers	Galvanized steel
Carpentry, furniture making	Eastern white pine, maple, birch, yellow birch, workplace mixtures
Dental laboratory workers, adhesive handlers	Acrylates
Plastics, epoxy resins workers	Anhydrides
Different industries	Formaldehyde

Appendix C

Number of positive and negative specific inhalation challenges (SICs) based on causal agent

Agent	*OA + OR*	*OR alone*	*OA alone*	*negative SICs*
High-molecular weight				
Flours	9	1	2	2
Other cereals	-	-	2	1
Animal epithelium	2	3	-	1
Guar gum	1	-	-	-
Tea	-	1	-	-
Cinnamon	-	-	-	1
Enzyme	-	-	-	1
Subtotal	**12**	**5**	**4**	**6**
Low-molecular weight				
Isocyanates	1	2	-	5
Formaldehyde	-	1	-	3
Acrylates	-	1	-	-
Alginate	-	1	-	-
Resins	1	2	-	1
Woods	0	2	-	1
Steel	-	1	-	1
Subtotal	**2**	**10**	**0**	**11**
Total	**14**	**15**	**4**	**17**

OA+OR, challenge positive for occupational rhinitis and occupational asthma
OR alone, challenge positive for occupational rhinitis alone
OA alone, challenge positive for occupational asthma alone

Appendix D

Copy of letter of approval of the study from the Ethics Committee, Hôpital du Sacré-Coeur de Montréal